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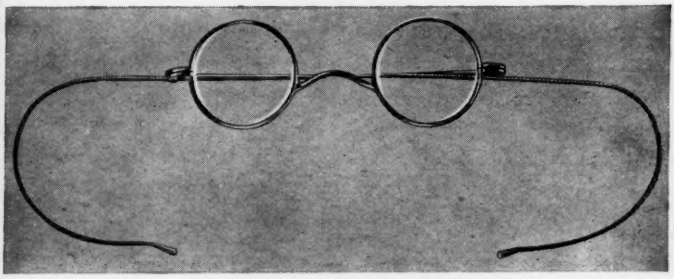
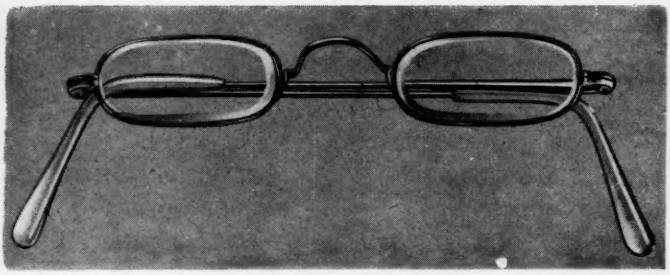


THE BISHOP-HARMAN LOUPE



THE MAYOU LOUPE

The two Loupes illustrated above are cheap and simple forms, giving adequate magnification and leaving a large free field. They can be worn over ordinary spectacles and are the lightest and simplest of all binocular Loupes. The upper illustration depicts the Bishop-Harman Loupe in which the circular lenses are in effect the two halves of a large sphere with the consequent prism base in. The alternative Mayou Loupe below is preferred by some as being more easy to wear and having a slightly larger field laterally.

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COMMUNICATIONS

INTRA-OCULAR PRESSURE IN PRIMARY CONGESTIVE GLAUCOMA*

BY

S. J. H. MILLER

From the Institute of Ophthalmology, London
Director of Research: Sir Stewart Duke-Elder

THIS investigation was undertaken at the Institute of Ophthalmology, London, the patients being drawn from a series of 100 individuals. All of them suffered from glaucoma characterized by a clinical onset consisting of periodic halos, with episodes of blurred vision and ocular pain. They formed a group of primary glaucomas in the adult, defined in this paper as congestive. Other characteristics of the patients in this group have been described in a previous paper (Miller, 1952). Narrow chamber angles, full peripheral and central fields of vision, and absence of cupping of the optic disk in the early stage of the disease are the main ocular features.

A Typical Early Case.—On June 29, 1951, a female patient aged 45 years was referred to the glaucoma clinic with the following letter:

> I should be grateful if you would accept this patient for investigation in the glaucoma clinic. The recent onset of halos is not convincing and I have been able to detect no positive evidence of glaucoma.

Eight weeks previously she had visited a cinema and after the performance complained of pain in the right eye with some blurring of vision. On the way home she noticed bluish rings round street-lights. Similar attacks had recurred at approximately weekly intervals, always in the evening after 8 p.m.

Examination revealed visual acuity of 6/5 right and left eye, shallow anterior chambers and narrow angles, no iritic atrophy, full fields of vision centrally and peripherally, negative dark-room and water-drinking tests, and an intra-ocular tension of 15 mm. Hg Schiötz in each eye. A 24-hour diurnal variation curve of the intra-ocular pressure was undertaken on two occasions with similar results. One of these is charted in Fig. 1. The negative results of all examinations could not outweigh the very typical history of attacks of halos occurring with blurring of vision and pain in the right eye, and arrangements were made for her to visit hospital when an attack was in progress. On September 25, 1951, she walked into the hospital at 11.30 p.m. complaining of halos seen with the right eye. Her intra-ocular pressure was found to be 44 mm. Hg right, and 20 mm. Hg left. No treatment was administered and next day the tonometer readings were 21 mm. Hg right and 21 mm. Hg left.

This case history shows the value of measuring the intra-ocular pressure in congestive glaucoma when symptoms are in evidence, and suggests that when the diagnosis is in doubt, a patient who complains of periodic halos should be instructed to report to a suitable centre for a tonometric reading during an attack, for the symptoms of early congestive glaucoma are nearly

* Received for publication October 13, 1952.

always worse in the evenings when consulting rooms and out-patient departments are closed. Two short case histories emphasize this point.

(1) Female, aged 35 years.—From the age of 22 years she had noticed periodic fogging of her left vision. The attacks were typical of congestive glaucoma, occurring always at night and accompanied by halos and ocular pain. She was examined many times, but always during the day, and she was assured, as many times, that her eyes were healthy: 6 weeks before she attended the Glaucoma Clinic she was carefully examined neurologically (including an EEG) and migraine was diagnosed. The diagnosis of congestive glaucoma was made when she was examined one evening by an ophthalmic surgeon during an attack. At this time her visual acuity was 6/5 right and 6/6 left and the fields of vision were full.

(2) Male, aged 49 years (diurnal variation curve Fig. 9*a*).—In the summer of 1948 he began to notice halos with both eyes at night. He was seen at 6-monthly intervals between 1948 and 1951. Each time his fields and tension were carefully examined and no abnormality was found. He was finally dismissed and told he was an "odd" case. At the time of diagnosis visual acuity was 6/5 in each eye and the fields were normal.

These cases demonstrate that an eye suffering from attacks of subacute congestive glaucoma may appear healthy and react normally between bouts of raised tension.

I have carried out 24-hour diurnal variation curves of intra-ocular pressure in a series of 25 early cases of proved congestive glaucoma most of whom had had no treatment. None of these patients complained of symptoms during the test. Twenty of these curves lay within normal limits and five showed minor deviations from normal. In congestive glaucoma the diurnal variation curve may be of no diagnostic value unless it is coincident with the appearance of symptoms. Fig. 1 gives an example of a typical curve showing no abnormality and Fig. 2 an example of a suspicious curve showing a minor abnormality.*

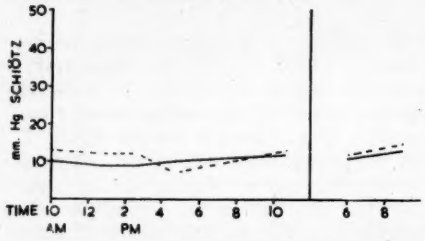

FIG. 1.—Normal 24-hour diurnal variation curve in a patient who was later proved to have congestive glaucoma.

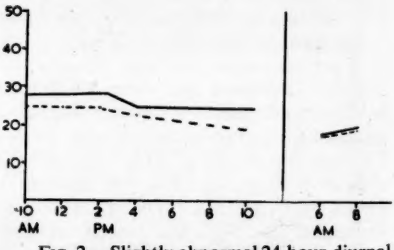

FIG. 2.—Slightly abnormal 24-hour diurnal variation curve in a patient with proved congestive glaucoma who had withheld miotics for 36 hours. No symptoms during this period.

Intra-Ocular Pressure during an Attack.—The onset of an attack of raised tension may take place quite dramatically and suddenly. I have been fortunate in witnessing several such attacks while examining established cases after miotics had been stopped for 24 hours; the results are seen in Fig. 3 (opposite).

* In all figures the tension of the right eye is recorded by an unbroken line, and of the left eye by a dotted line. The vertical line breaking the curves indicates that observations were discontinued while the patient was asleep.

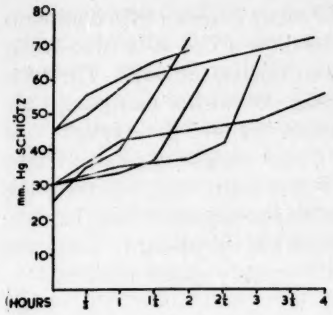

FIG. 3.—Rapid rises of intra-ocular pressure in six patients with established congestive glaucoma who had withheld miotics for 24 hours. Symptoms of halos, blurring, and ocular pain appeared, and increased with the rise in tension.

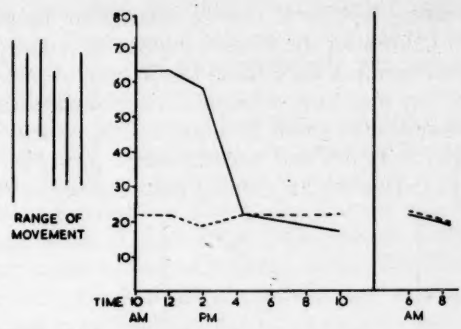

FIG 4.—Spontaneous fall in tension in an untreated patient. (Same patient as Fig. 1).

A spontaneous fall of tension in an untreated case moves over as wide a range (Fig. 4). It will be observed that these sharp changes take place over a period of 4 hours or less and emphasize the futility of an isolated Schiötz reading. In all cases the patients were aware of halos, blurring of vision, and a feeling of fullness or pain in the eye when the intra-ocular pressure was at its height, and these symptoms were relieved when the tension fell spontaneously or with miotics. As far as I have observed, symptoms in an untreated case of congestive glaucoma always indicate an abnormally raised ocular tension, and the absence of symptoms in an untreated recent case indicates that the intra-ocular pressure has remained within, or not far beyond, normal limits during that period. The symptoms and the attacks of raised intra-ocular pressure are contemporaneous and episodic.

Spacing of Attacks.—Early in the course of the disease congestive attacks occur infrequently with long periods of freedom. Three typical early cases had attacks at the following times:

(1) *Female, aged 57.*—Feb. 8, April 9, May 1, June 5 and 23, August 21 and 25.

(2) *Female, aged 45.*—Five attacks between June 4 and 14; six attacks between July 8 and 22; attacks on July 29, 30, and 31, and on August 3, 7, 8, and 9.

(3) *Male, aged 45.*—Jan. 7, 9, 12, 16, 18, 21, 25, 26, and 30; Feb. 7, 11, 18, and 19; March 3, 5, 6, 10, 11, and 17.

The attacks become more frequent as the disease progresses until they occur nearly every night, and the onset of symptoms occurs earlier in the day. Fig. 5*a* (overleaf) shows a curve from a patient who had reached the stage of developing attacks every evening.

Precipitating Factors.—The cinema and television are the commonest provokers of attacks and it is so rare for a patient with congestive glaucoma to deny the detrimental effect of the cinema on visual acuity that I would question my diagnosis in the face of it. What the precipitating factor in

visiting the cinema may be is not clear, because many patients who complain of halos after the theatre, cannot be induced to show a rise of tension when enclosed in a dark room for 30 min. to one hour during the day. The time of day may have some effect, although halos may occur after matinées; they disappear in about 20 minutes if the patient comes out into the daylight, but they continue and become more prominent if the patient comes out into the dark after an evening performance. It would seem that, whatever the precipitating factor may be, daylight has the power to lower the abnormally raised tension.

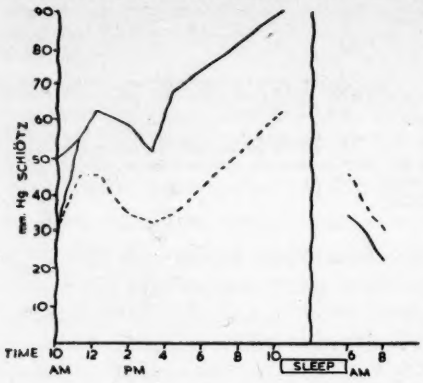

FIG. 5(*a*).—24-hour diurnal variation curve in an untreated patient who saw halos each night.

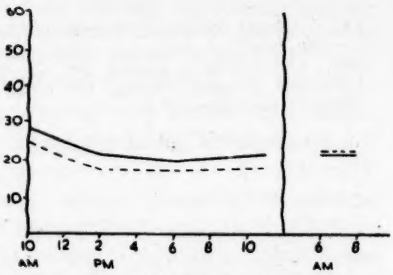

FIG. 5(*b*).—24-hour diurnal variation curve to show the effect of miotics. (Same patient as 5*a*).

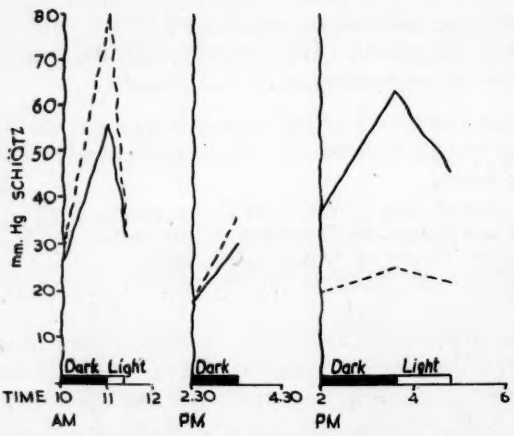

FIG. 6.—Three dark-room tests showing rapid rises of tension in all cases, and sudden falls in two cases on exposure to light.

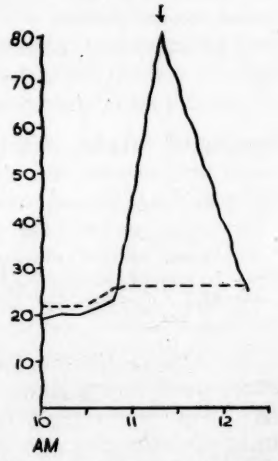

FIG. 7.—Spontaneous rise in tension in an untreated patient who was apprehensive at the time of examination. At the arrow, miotics were instilled to counteract the raised tension and remove the blurred vision.

There is no doubt that, in some cases, darkness of itself has a very dramatic effect, as in the three cases shown in Fig. 6, and it is common for patients to note the seasonal variation in the incidence of their symptoms, the attacks being more frequent and severe during the winter months.

Another common provocative agent is an emotional crisis. Attacks are described following a disagreement with a neighbour, on receiving sudden news by telephone of illness in the family, on excitement at a game of cards, before an examination, at the end of a hectic day, and so on. Such examples could be multiplied many times. Fig. 7 shows the rapid rise of intra-ocular pressure in a very nervous woman who was referred to the Glaucoma Clinic and who, at this visit, was very much afraid of encountering someone for whom she had a strong (though unjustifiable) dislike.

Prolonged visual concentration may precipitate attacks, especially if carried out under bad lighting conditions. Fig. 8(*a*) shows a sudden rise in a patient who spent the morning between 10 a.m. and 12 noon reading in a semi-dark corridor. Fig. 8(*b*) shows her diurnal variation curve taken on a different day.

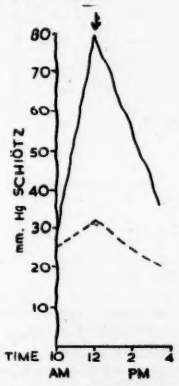

FIG. 8(*a*).—Spontaneous rise in tension in an untreated case after a period of reading in a poor light. At the arrow, miotics were instilled.

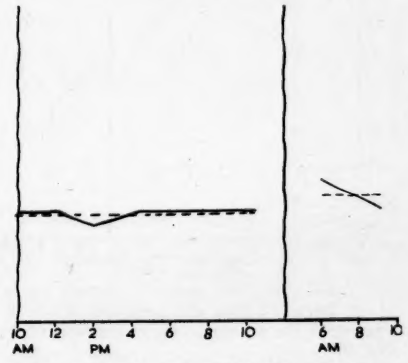

FIG. 8(*b*).—Diurnal variation curve of the same case taken on a different day.

Some women suffer from regular attacks during the pre-menstrual or menstrual period.

Relieving Factors.—There are also factors which tend to lower a raised tension, chief of which are sleep and rest. All patients, until very late in the course of the disease, state that their eyes are normal in the morning. Fig. 9*a* (overleaf) shows the effect of a night's sleep on an untreated case of congestive glaucoma of some 3 years' duration. Many patients are so aware of the beneficial effect of sleep that they modify their daily habits accordingly and sleep in the afternoon or in the early evening, and others

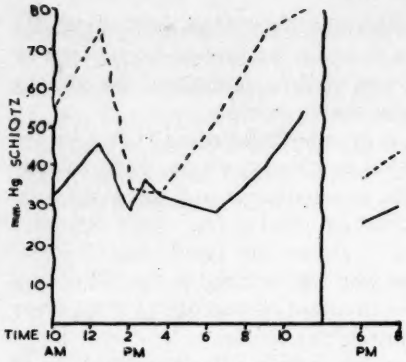

FIG. 9(*a*).—24-hour diurnal variation curve in a patient with untreated congestive glaucoma who had symptoms on most nights, to show the effect of sleep on the intra-ocular pressure.

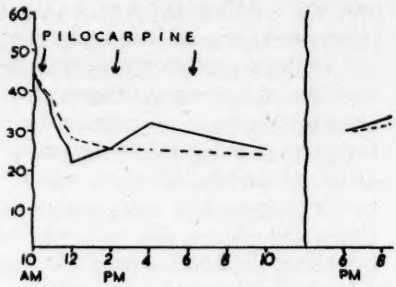

FIG. 9(*b*).—24-hour diurnal variation curve in a case of congestive glaucoma showing that miotics thrice daily may be inadequate therapy. (Same patient as in Fig. 9*a*).

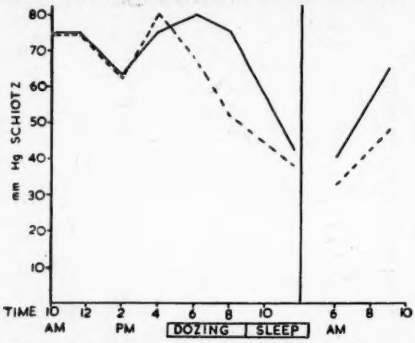

FIG. 10(*a*).—24-hour diurnal variation curve in an untreated case to show the effect of sleeping in the evening. (Same patient as in Fig. 10*b*).

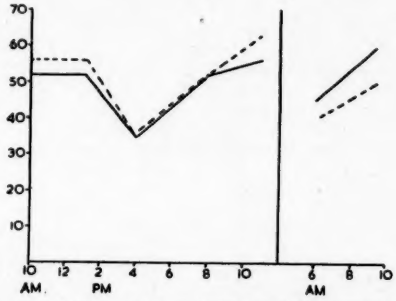

FIG. 10(*b*).—24-hour diurnal variation curve in a case of congestive glaucoma showing an uncontrolled tension despite miotics taken on a day when the symptoms were marked. (Same patient as in Fig. 10*a*).

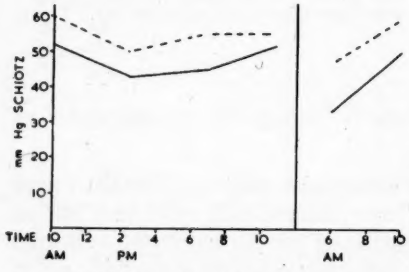

FIG. 11.—24-hour diurnal variation curve in a late untreated case to show the slight effect of sleep.

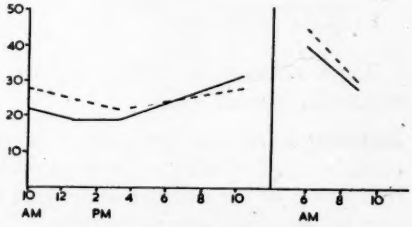

FIG. 12.—24-hour diurnal variation curve in a patient with established glaucoma who had withheld miotics for 48 hours. The patient gave a history of halos in the morning on rising.

adopt the philosophy of a quiet life at all times. Fig. 10(*a*) shows the effect of sleeping in the evening between 6 and 10 p.m. As the disease progresses the effect of sleep is less (Fig. 11) and the very occasional patient who complains of halos in the morning has a raised tension on rising (Fig. 12); but in the vast majority of cases sleep acts as balm to the eyes of those suffering from congestive glaucoma. "Incidentally I am sleeping better which to me accounts for the improvement", is a typical quotation from a patient's letter.

We have already seen that daylight will lower the abnormally raised tension (Fig. 6), but I have yet to find a patient who has noted this effect and applied it empirically as a therapeutic measure. An attack arouses a desire for complete rest both local and general, which is fulfilled by sleep and recumbency.

The effect of miotics is shown in Fig. 5(*b*). A successful iridectomy (Fig. 13), or a corneo-scleral trephine (Fig. 14), is as effective in the control of intra-ocular pressure; and an unsuccessful trephine shows the characteristic curve of an untreated case (Fig. 15).

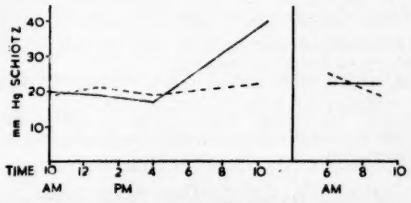

FIG. 13.—24-hour diurnal variation curve in a patient with established congestive glaucoma who had withheld miotics from the right eye for 48 hours. The left eye had undergone a broad iridectomy and its tension was stable without the aid of miotics.

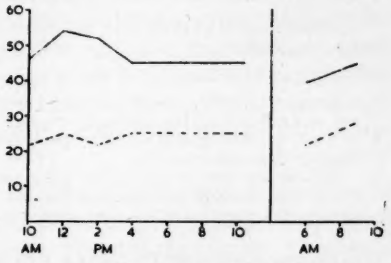

FIG. 14.—24-hour diurnal variation curve in a patient with established congestive glaucoma who had withheld miotics from the right eye for 24 hours. The left eye had undergone a trephine and its tension was stable without the aid of miotics.

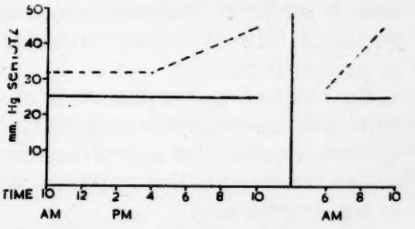

FIG. 15.—24-hour diurnal variation curve in a patient with congestive glaucoma who had undergone a trephine in the left eye. The trephine was not draining.

Progress of the Disease.—Most patients with congestive glaucoma who have been examined at the Institute are at first controlled on miotics which are used on waking, before leaving home for work, at lunch time, on arriving back home, and on retiring, making five instillations in all. There is good reason to think that a miotic given conventionally thrice daily is not enough. Fig. 9(*b*) shows a curve of a patient who used pilocarpine at 10.10 a.m., 2.20 p.m., and 6.10 p.m. The morning

tension (before treatment) is above normal on both days when the effect of the drug instilled the previous evening has worn off. Once a patient has used miotics, sleep would appear to be less effective in lowering tension.

The best guide as to the efficacy of treatment in an early case may be provided by an intelligent patient who reports the occurrence or absence of symptoms. It must be pointed out, however, that in advanced cases miotics occasionally mask symptoms without controlling the tension so that a follow-up examination of a patient on treatment must include Schiötz readings as well as enquiries as to the incidence of symptoms.

A majority of the cases progresses despite miotic therapy, and surgery becomes necessary, rarely because of a sudden acute attack, but usually because of periodic raised tension with symptoms despite miotics (Fig. 10*b*) or occasionally because of high tension sustained throughout the 24 hours despite good miosis, excellent visual acuity, and absence of symptoms. These findings are in accordance with Reese's conclusions on the rise of base-pressure as the disease advances (Reese, 1948).

A letter from a patient who was having periodic attacks despite miotics, describes the symptoms which call for surgery. His diurnal variation curve, taken on August 17, 1951 is shown in Fig. 2.

> January 14, 1952. On Friday last I went to the dentist (evening) and when I came out my eye was rather bad, but my sight was satisfactory on Saturday morning.
>
> I had another attack on Saturday evening, and to-night (Sunday) it is coming on again after writing this letter.
>
> This makes five or six attacks since September 14. These attacks are much milder than before having drops and also less frequent. It appears that I cannot concentrate or read for any lengthy period without a recurrence of the trouble.

Comparison of the Clinical Features and Variations in Intra-Ocular Pressure of Congestive and Simple Glaucoma

The division of glaucoma in the adult into two separate entities, congestive and simple, is largely based on clinical features. Congestive glaucoma tends to occur in women, affecting eyes with narrow chamber angles and with a refraction more hypermetropic than their counterparts in simple glaucoma. The latter occurs in either sex, affecting eyes with wide, medium, or narrow angles.

The mode of onset is different in the two types, having an acute or subacute pattern in the congestive group, with periodic attacks of halos, ocular pain, and blurring of vision, and an insidious, non-specific onset in the non-congestive group. The diagnosis may even be made before symptoms arise in simple glaucoma.

At the time of diagnosis, the visual fields in congestive glaucoma are usually unaffected, whereas central field changes are an early and valuable sign of simple glaucoma. Cupping of the optic disk is absent in early congestive glaucoma and is always established (either pathological or physiological) by the time the diagnosis of glaucoma simplex is made.

Congestive glaucoma is diagnosed at an earlier age and at an earlier stage

in the course of the disease than is simple glaucoma so that the threat to vision is less. Finally, the individuals affected with glaucoma show a difference in their mental outlook. The congestive is often a conscientious perfectionist striving to maintain high standards and to win for himself or herself a respected place of responsibility in the community. Such characteristics are less evident among patients with simple glaucoma who are older, more philosophical, and passive (Armstrong, 1952).

When a study is made of the intra-ocular pressure and its variations, it is suspected that the difference between the two groups is possibly fundamental. The rises in intra-ocular pressure in congestive glaucoma are periodic. At first the attacks are spaced well apart, last for a few hours in the evening, reach their maximum before retiring, and are relieved by sleep. As the disease progresses they become more frequent, begin earlier in the day, last longer, and may even continue for several 24-hour periods. The diurnal variation curve of the intra-ocular pressure in simple glaucoma is a characteristic of the individual and will repeat itself faithfully from day to day but (as a general rule) the intra-ocular pressure tends to fall in the evenings (Langley and Swanljung, 1951). The variation between the highest and lowest pressure in congestive glaucoma tends to lessen with progress of the disease, due to a rise in the base-pressure (Reese, 1948). In simple glaucoma, on the other hand, the higher the maximum tension the greater the variation (Langley and Swanljung, 1951).

A study of the factors which influence intra-ocular pressure reveals the marked effect of the environment in congestive glaucoma and its apparent impotence in influencing the intra-ocular pressure in simple glaucoma. Thus darkness and the cinema, changes in emotional tone, fine visual work, and sometimes the hormonic changes of the female sexual cycle may produce sharp rises in pressure in congestive glaucoma, and such rises can be allayed or reduced by sleep and rest, or by the influence of daylight. In simple glaucoma on the other hand, the intra-ocular pressure is unaffected by these factors and shows no response to alterations in blood pressure, body posture, size of pupils, or the ingestion of food (Langley and Swanljung, 1951).

Lastly, the destruction of the eye as a seeing organ, measured by progressive field loss, is related in congestive glaucoma to the number and duration of the attacks of raised pressure, whereas in simple glaucoma the fields may be gradually and relentlessly destroyed unaccompanied by a high intra-ocular pressure.

Although these two groups of primary glaucoma in the adult have many distinct features early in the course of the disease, the later stages are barely distinguishable. Thus, cases of subacute intermittent congestive glaucoma may develop field loss in every way comparable to that seen in simple glaucoma, the optic disk may become cupped, the ocular tension may remain high and steady with little in the way of episodic variation, or may fall at

night and rise in the morning; sleep loses its effect and daylight can no longer restore the eye to normal. The late case of simple glaucoma may develop halos with blurring of vision due to corneal oedema, and if the angle of the anterior chamber is narrow, peripheral anterior synechiae may be produced. In such cases, in the absence of an accurate history, it is quite impossible to state whether the patient is suffering from congestive or simple glaucoma. It may be for this reason that some are sceptical of the existence of the two syndromes (Lloyd, 1952).

Summary

(1) Evidence is given to show that the periodic symptoms of early congestive glaucoma are always associated with raised intra-ocular pressure and that between such episodes the eye may appear healthy, react normally to all tests, produce no symptoms, and have a normal intra-ocular pressure.

(2) The factors precipitating and relieving the attacks are discussed and described with reference to actual cases. Precipitating factors are the cinema, television, darkness, emotional crises, and prolonged visual concentration. Relieving factors are sleep, rest, daylight, miotics, a filtering operation, and iridectomy.

(3) The changing pattern of the variations in tension is followed as the disease progresses.

(4) The clinical features and variations in intra-ocular pressure of congestive and simple glaucoma are compared and contrasted.

REFERENCES

ARMSTRONG, P. (1952). *Med. Press*, **228**, 166.
LANGLEY, D., and SWANLJUNG, H. (1951). *British Journal of Ophthalmology*, **35**, 445.
LLOYD, J. P. F. (1952). *Brit. med. J.*, **1**, 712.
MILLER, S. J. H. (1952). *Ibid.*, **1**, 456.
REESE, A. B. (1948). *Amer. J. Ophthal.*, **31**, 25.

Brit. J. Ophthal. (1953) **37**, 11.

EXPERIMENTAL THIAMIN DEFICIENCY AS A CAUSE OF DEGENERATION IN THE VISUAL PATHWAY OF THE RAT*

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THAT the fundamental alteration in the visual pathway in thiamin deficiency might be biochemical and not cellular is an opinion that has been freely expressed; yet, as there is little doubt that such a deficiency leads to a widespread degeneration of the central vestibular neurones (Swank and Prados, 1942), it seems reasonable enough to expect that the visual neurones might be similarly affected.

It is surprising, in view of the possible relationship between thiamin and nutritional amblyopia, to discover how little experimental work on the subject has been performed. Most of the pioneers in this field were, of course, under the impression that thiamin filled the role earlier assigned to the hypothetical anti-beriberi vitamin. They believed wrongly that they were inducing only a thiamin deficiency by feeding birds with polished rice. Optic nerve degeneration in experiments of this nature is described by Barletta (1932) and Marchesini and Papagno (1935).

Involvement of the visual pathway in animals on a diet deficient only in the heat labile member of the B complex was noticed by Prickett (1934) in rats, and by Peters (1934) in pigeons.

The blindness which they describe, however, was a subjective finding in the terminal stages of an acute experiment. There might, then, be an explanation for it other than a cellular degeneration of the visual neurones. When animals are severely deficient, they become no longer interested in their surroundings, and need a deal of arousing, fatigue and lethargy being dominant signs. For this reason, subjective investigation of an animal's response to visual stimuli in the terminal stages would appear to be of slight value. The rest of Peters' work, however, is of such a high order that perhaps more stress has been laid upon this observation than was intended.

The series of painstaking experiments on thiamin deficiency undertaken by Swank and his various collaborators constitute the main argument in favour of thiamin being an antineuritic vitamin. In addition, Swank and Prados (1942), describe degeneration of the optic fibres within the central nervous system in an avian thiamin deficiency, induced by administering autoclaved yeast and a low protein diet. This seems an excellent paper, and most of the criticism it has aroused appears not to be justified.

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Although primarily interested in the vestibular system, Swank and Prados noted that the central terminations of the optic fibres in the deficient birds were either grossly thickened or fragmented; in the severe cases this was associated with sclerosis of the related cells within the optic lobes. We cannot of course consider the optic lobe of the pigeon as being the homologue of the lateral geniculate body in man. Primitive geniculate bodies are already present in teleosts, for example, which possess optic lobes in addition.

One criticism levelled against Swank by Shaw and Phillips (1945) was that food placed in the pigeon's crop is not always ultimately swallowed and digested. More serious is the criticism that the diet lacked many amino acids not required by mammals but essential to birds. Could absence of these be the causative factor in producing degeneration? Prados and Swank (1942) had the last word: they produced the same type of degeneration in mammals (kittens), but unfortunately their claims and conclusions are there less clearly expressed.

Such, then, is the meagre positive evidence that exists.

A somewhat larger number of workers interested in this problem, who describe experiments in which they could find *no* significant degenerative changes within the visual pathway in thiamin deficiency, includes Engel and Phillips (1938), McDermott and others (1943), and Leinfelder and Robbie (1947). One must mention, too, the positive opinions of Zimmerman (1943) whose brilliant work on canine nutritional neuropathies is well known to workers in this field; there is no specific experiment of his own devoted to a study of the visual path, but he stated that he had never been convinced that optic atrophy occurred experimentally in dogs, pigeons, or rats as a result of thiamin deficiency.

This brief account of the relevant literature shows that the evidence is scanty and extremely conflicting; but the various discrepancies and disagreements proved helpful in planning the present experiments.

Methods

In all our experiments, rats between 50–100 g. in weight were preferred. The individual weights are given in detail below.

The animals were weighed on the first day of the institution of the experimental diet, at weekly intervals, and on the last day. On each occasion, the weighing took place before feeding. At the same time, the opportunity was taken to examine the eyes, skin, fur, gait, and posture. This was done in daylight on a raised examination table. Towards the termination of each experiment a general examination was undertaken *daily*.

The animals were housed in individual cages fitted with wide wire mesh floors. The cages were shaded, draught-free, and kept in a room of constant temperature (65–75° F.).

The principle of paired feeding was adopted, the control animal in nearly all cases being from the same litter.

Force-feeding was not used. In the chronic deficiencies, we learned by trial experiments how to prevent anorexia. In those few cases in which loss of appetite

persisted, we feel paired feeding adequately covered the probable effects of inanition. In our experience, anorexia is not such a striking symptom in chronic thiamin deficiency as it appears to be in a deficiency of the entire B complex (Drummond and Marrian, 1926). The appetite could be brought back by the administration of as little as 10 μg. of thiamin hydrochloride. It rarely reached a severe degree (*i.e.*, less than 2/3 eaten) until the weight had fallen to its original level. Even then, by careful nursing, the animals could be made to eat as much as 7.5–10.0 g./day per 100 g. body weight, which is far from starvation level in a rat exhibiting a marked disinclination to exercise.

In the acutely deficient rats, so rapid was the onset of severe symptoms that force-feeding—a matter of great difficulty in rats—led to sudden death, and was therefore abandoned. In such cases, having previously carefully investigated the morphological lesions resulting from inanition, it was a simple matter to take them into account in the final assessment.

The criterion taken as being most characteristic (in rats) of a chronic thiamin deficiency was a reduction in heart rate. When this fell to the neighbourhood of 300 beats/min. it was felt that the animals were deficient whether gross clinical manifestations were evident or not.

The bradycardia of experimental thiamin deficiency is generally accepted as being pathognomonic. It cannot be caused by inanition unless this is very prolonged, which was never the case in our experiments. It was, moreover, never found in any of the control animals. Without altering the diet, the bradycardia can be eliminated by administering 1 mg. intraperitoneal thiamin hydrochloride. If the rate fell below 200 beats/min., we were less successful in obtaining recovery.

The cause of this bradycardia is not known. Drury, Harris, and Maudsley (1930), though they produced in some rats a slight increase in heart rate by vagal section, failed to restore it to the normal values. One must presume, therefore, that it is of sinus origin. Our method of recording the heart rates was essentially that described by Harris and his colleagues, and the procedure they described was followed as carefully as possible. It appears that when the recordings are made under standard conditions, conclusive evidence may be obtained by comparing the figures with those for the control rats, whose heart rates are recorded at the same time.

In acute thiamin deficiency, however, bradycardia could not be taken as an index of the success of the experimental diet, for this appears in our experience to develop only in the terminal stages, when the animals are moribund. The nervous disorders characteristic of chronic deficiency become manifest sometimes before, usually after, the appearance of bradycardia. In acute deficiency, they always coincided, and so, in the latter, it was the nervous symptoms which determined the termination of the experiment. In short, the acutely deficient rats were killed when they were seen to be dying, and the chronically deficient when bradycardia was in the neighbourhood of 300 beats/min.

On termination of the experiments, the rats were killed by decapitation under urethane. The brains, optic nerves, and eyeballs were then removed and fixed *within 10 minutes* in 10 per cent. neutral formalin. Such speedy fixation is essential if autolytic distortions are to be prevented. Some twigs of sciatic nerve taken at random from each group were similarly treated. As the primary interest was in the visual path, it was not possible to investigate each sciatic nerve in every case in its entirety.

The pathological alterations in the peripheral nerves in thiamin deficient animals do not appear to be as clear-cut as the clinical manifestations described above. (It is this finding which suggests that beriberi is not due solely to an absence of thiamin). According to numerous authors (Prickett, 1934; Davison and Stone, 1937; Engel and Phillips, 1938; Prickett, Salmon, and Schrader, 1939) examination of the peripheral nerves of rats fed on diets containing autoclaved yeast has revealed no significant morphological differences from those of control animals. The slight changes which occurred are ascribed to inanition. Berry, Neumann, and Hinsey (1945) placed cats on a thiamin-free diet for as long as 116 days but found no trace of degeneration in the peripheral nerves, and the same conclusion with regard to swine was reached by Follis and others (1943) and by Wintrobe and others (1944).

This fact is not, we feel, generally appreciated, but the evidence is too strong to ignore. To have used peripheral nerve preparations as a means of controlling the experiment, therefore, would appear somewhat pointless.

Constitution of Diets

(1) Daily Caloric Requirements.—A rat of 75 g. will thrive on approximately 10 g. food daily; a rat of 150 g. requires 15 g., and rats above 200 g. vary in their demands. All rats in the experiment were less than 150 g. in weight, and 15 g. food was fed to each irrespective of weight. Thus, no rat, control or otherwise, was fed at too low a level. It was considered quite normal if less than 5 g. of the daily ration was left uneaten by rats of 75 g. or less.

(2) Composition of Diets.—The " stock " diet was made up as follows:

(*i*) *Casein*	15	
(ii) Salt mixture	4	
(*iii*) *Glucose*	70	100
(*iv*) Water soluble vitamins (W.S.V.)	10	
(*v*) Fat soluble vitamins (F.S.V.) ...	1	

(3) Details of Dietary Components

(*i*) *Casein* (*lactic casein, unextracted*)

Moisture	10	
Fat	*2.1*	
Nitrogen	13.5	15
Calcium	0.04	

It should be noted that the composition of the diet is based on dry weights, an allowance being made for the 10% of water present in casein.

The quantity of protein is low, of course, as the proportion of carbohydrate is required to be high. This precipitates thiamin deficiency (Yudkin, 1951). The protein is quite sufficient, however, for growth. It is vitamin-free.

(*ii*) *Salt Mixture* (g.)*

Sodium chloride	22
Calcium phosphate ...	130
Potassium citrate	*125*
Magnesium sulphate ...	30
Iron citrate	5
Trace mixture	0.7
	312.7

Trace Mixture

Potassium iodide	*12*
Sodium fluoride	10
Manganese sulphate ...	2
Cuprous iodide	1
Potash alum	1
Zinc sulphate	*1*
	27

* This corresponds to DL6, a salt complex prepared by Glaxo Laboratories, Greenford, Middlesex, and was purchased from them. In the initial planning of the diets, the helpful advice of Dr. W. F. J. Cuthbertson of that same laboratory is gratefully acknowledged.

The manganese and magnesium proportions are higher than most workers prescribe to ensure good growth, and the normal excitability of the nervous system. There is nothing unusual in the quantities of the other salts present.

(*iii*) *Glucose.*—That incorporated in the diet was of the pure medicinal variety.

(*iv*) *Water Soluble Vitamins*

Choline chloride	10.0 g.
Inositol...	1.1 g.
Nicotinic acid	0.5 g.
Calcium-*d*-pantothenate	0.5 g.
Pyridoxine hydrochloride	*40.0 mg.*
d-Biotin	1.0 mg.
Folic acid	1.0 mg.
Para-aminobenzoicacid	0.375 g.
Distilled water to	250 ml.

Riboflavine, 150 mg., was then dissolved in the least amount of boiling 5 per cent. acetic acid, shaken in 50 ml. non-methylated 95 per cent. alcohol and added. Finally, distilled water brought the total volume up to 500 ml.

The daily dose of W.S.V. was 1 ml. per rat.

The absence of ascorbic acid from this complex is not an oversight. Rats need not be given vitamin C, as they synthesize it readily in the intestine. On a diet deficient in this factor considerable quantities are found in the livers, even after a long period (Coward, 1947).

If the relationship of riboflavine to thiamin is to be investigated, the former vitamin can be made up separately, the composition of W.S.V. being adjusted accordingly. Riboflavine itself is administered at the same level (150 mg. in 500 ml.). The daily dose per rat is 1 ml. as in the original W.S.V.

The full maintenance dose of thiamin required by rats above 50 g. in weight is in the region of 10 μg. a day. Woolley and White (1943) claim that mice require 2 μg.; Arnold and Elvehjem (1938), that chicks require 10 μg.; and Swank and Bessey (1941) that pigeons require 20 μg.

Nevertheless, we administered thiamin at the extremely high level of 500 μg. daily to the control animals, giving 5 μg. only to the deficient, as follows:

(*a*) *Full maintenance dose* (*thiamin full*)	(*b*) *Minimal maintenance dose* (*thiamin minimal*)
Thiamin hydrochloride 250 mg.	Thiamin hydrochloride ... 5 mg.
Distilled water to 500 ml.	Distilled water to ... 500 ml.
Daily dose per rat 1 ml. (0.5 mg.)	*Dose, when directed, 0.5 ml. (5 μg.).*

The detailed administration is given later with each experiment.

(*v*) *Fat Soluble Vitamins*

β-carotene (1.2×10^6 i.u.)	5 mg.
Calciferol (0.2×10^6 *i.u.*)	5 mg.
α-tocopherol acetate	2 mg.
Arachis oil to	100 g.

Daily dose per rat 0.1 ml. (about 3 drops).

Vitamin K (2 methyl-1, 4-naphtha-quinone) was not included, for no changes have been detected in the tissues of animals deficient in vitamin K, apart from the physiological defects associated with haemorrhage.

Ferraro and Roizin (1943), in an interesting paper on vitamin K deficiency in rats, describe the presence of multiple haemorrhages in the brain. Best and Taylor (1950), however, maintain that it is not possible to induce a haemorrhagic tendency in rats owing to the high degree of synthesis going on in the intestine.

As the absence of vitamin K does not affect the central nervous system, it was omitted, a practice in keeping with that of other workers.

Histological Techniques

The eight different histological techniques employed are shown in Table I. A full description with their inherent fallacies has been given elsewhere (Rodger, 1951). It should be stressed that before the experiments here described were performed, a year was spent in becoming familiar with the anatomy of the rat visual path, the histological methods of choice, and the appearance of the visual neurones in various known diseases.

TABLE I

HISTOLOGICAL TECHNIQUES

Part of Visual Path	(1) Nissl	(2) Giemsa	(3) Triple	(4) Polarized Light	(5) Marchi	(6) Weigert-Pal	(7) Loyez	(8) Silver Nitrate
Retina	X	X	X					
Optic Nerve { Axons ...				X				X
Optic Nerve { Myelin				X	X	X	X	
Optic Tract { Axons ...				occasionally				X
Optic Tract { Myelin				occasionally	X	X	X	
Lateral Geniculate Body { Cells ...	X	X						X
Lateral Geniculate Body { Processes								
Lateral Geniculate Body { Myelin							X	

The rat visual pathway is easily dissected. The cerebral hemispheres are removed by hand. Then, splitting the chiasma, and laying the brain on its lateral side, one may excise the optic nerve, half-chiasma, tract, and lateral geniculate body in one piece. Portions of the thalamus and cerebral peduncle are included. The visual fibres leave the tract to synapse in the dorsal nucleus of the lateral geniculate body. By this dissection, an opportunity is afforded of studying the nerve, tract, and dorsal nucleus in the same section. The section may be described as representing the anteroposterior and dorsoventral diameters, and as it is possible to examine the entire length of the nucleus by serial sections, observations may be also made in its medio-lateral diameter.

Plan of Experiments

In several trial experiments, it was found that the onset of nervous manifestations of acute deficiency began very suddenly—within 24 hrs or so of the appearance of anorexia and bradycardia. We wondered, therefore, if these manifestations might not have resulted from inanition. Furthermore, if anatomical damage had caused the nervous disorders, it might be that this, too, depended on caloric inadequacy.

These possibilities, unlikely though they seemed, and the further desire to discover whether the nervous symptoms were due to lack of calories or lack of vitamins, led to the framing of the first two of the six following experiments:

(1) Caloric inadequacy without exogenous vitamins.
(2) Caloric inadequacy associated with full vitamin intake.

(3) Acute deficiency in thiamin due to administration of the analogue.
(4) The same, recovered.
(5) Reduced thiamin intake associated with a high carbohydrate diet, inducing a chronic deficiency.
(6) The same, recovered.

Results

(1) Caloric Inadequacy without Exogenous Vitamins

Diet.—

Potato starch	70	100
Wheat straw pulp	20	
Agar-sucrose	10	

Clinical Behaviour.—On this diet, fed *ad libitum*, six rats (average weight 200 g.) died at the end of 11 days. They were perfectly healthy until the morning of the 10th day when they were seen to be very inactive, and to have assumed a crouching position. They could be roused only with difficulty, their movements were inco-ordinated, and their postural sense appeared diminished. Next morning they had violent convulsions while on the examination table and within half an hour were dead.

Pathological Observations.—Vacuolation of the ganglion cells of the retina and geniculate body was the only cytological change found. As vacuolation of the retinal cells is a very common artefact, more common than swelling, we are inclined to consider that this is the explanation of the finding.

The myelin sheaths viewed by polarized light were hazy in outline and their substance somewhat granular (Fig. 1), and this was also true of the sciatic twigs, but Loyez and Marchi stain revealed no abnormality. No sign of any degeneration involving the nerve fibres was found.

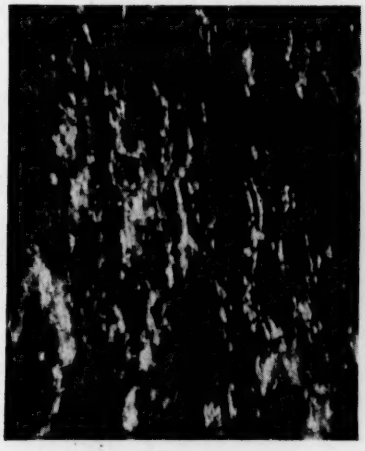

FIG. 1.—Granular isotropism of optic-tract myelin sheaths in caloric inadequacy without exogenous vitamins. Polarized light ×250.

(2) Caloric Inadequacy associated with Full Vitamin Intake

Diet.—

Potato starch	70	100
Wheat straw pulp	20	
Agar-sucrose	10	
W.S.V. (less thiamin)	6 ml.	

Clinical Behaviour.—Six rats of average weight 160 g. and members of the same litter were fed the usual 15 g. daily for 24 hrs. They were then divided into two groups:

(A) remained on the same diet
(B) received 2.0 mg. thiamin (i.p.) daily in addition.

On the 18th day, the three rats in Group A and one of the rats in Group B died. Two days later the remaining two rats in Group B, now moribund, were killed. The manner of death in those permitted to die was exactly as described in Experiment 1.

Pathological Observations.—There were no essential differences between the two groups, A and B.

In the retina, the outline of many of the cells was indistinct, the cytoplasm staining homogeneously, and the nucleus containing dark-stained granules.

The geniculate cells exhibited signs of severe somatic disorder. The Nissl bodies in many cells were clotted and darkly stained. The cell outlines were frequently badly distorted. Some of the astrocytes were swollen, and there were many hypertrophied cerebral histiocytes (rod cells) with dark-staining nuclei. Long oligodendrocytic chains lay in the fibre pathways.

The nerve fibres themselves were tortuous, but not otherwise distorted. The endings were unaffected.

The myelin sheaths revealed more positive changes than in the previous series, but, in view of the advanced cellular damage present, these changes were much less than we expected. There was a similar slight degree of demyelinization in the sciatic nerves, revealing itself in polarized light in both instances as a granular isotropism.

(3) Acute Deficiency in Thiamin due to Administration of the Analogue

Diet.—

Stock (Glucose + W.S.V.) ...	15 g.
*Pyrithiamin	100 μg.
Thiamin minimal	5μg.

Clinical Behaviour.—The weights and heart rates are shown in Table II.

TABLE II
EXPERIMENT 3 (DURATION 17 DAYS)

Rat No.	Weights (g.)			Heart Rates (beats/min.)			Disposal
	Initial	Final	Difference	Initial	Final	Difference	
1	90	80	−10	500	250	−250	Killed
2	80	87	+7	500	240	−260	Killed
3	75	95	+20	510	310	−200	Killed
4	75	75	0	500	—	—	Killed
5	75	75	0	500	—	—	Killed
6	85	90	+5	500	300	−200	Killed
7	80	77	−3	500	—	—	Killed
8	117	100	−17	400	200	−240	Died during recording
9	100	102	+2	480	300	−180	Killed
10	85	88	+3	500	—	—	Killed
11	92	96	+4	490	—	—	Killed
12	90	89	−1	460	—	—	Killed

* As this was not available in Great Britain at the time, this was generously supplied by the Research Department, Merck and Company, Rahway, New Jersey. It was prepared in their laboratories, and renamed Neopyrithiamine, and we found it most effective.

On the 17th day all the animals were found to exhibit the same clinical picture. When they were picked up by the tail a convulsion appeared, and, on recovery, spasticity of the hind legs was marked, and occasionally the animal fell over sideways in spasm. Both sides seemed equally affected. Some of the animals were ultimately (minutes) unable to move, assuming what later proved to be a characteristic pose, lying flat on their abdomens with their limbs extended outwards. Spontaneous convulsions appeared in two of them. Anorexia was first seen about 36 hrs before death.

Pathological Observations.—There was cloudy swelling of the retinal bipolar and ganglion cells (Fig. 2). This is of doubtful significance.

The optic nerve fibres were slightly more tortuous than normal.

There were no other signs of degeneration in retinae, nerve fibres, myelin sheaths, or geniculate bodies.

A few of the twigs of the sciatic nerve revealed marked degeneration of myelin (Fig. 3), except in Rats 3 and 5, where no abnormality was discovered in the twigs removed for examination.

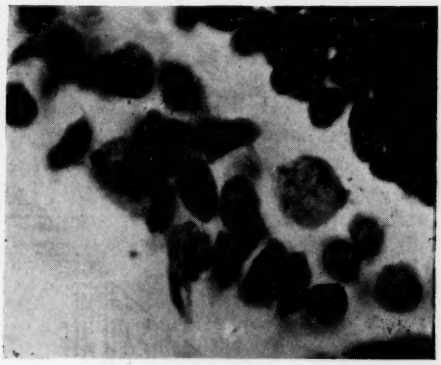

FIG. 2.—Cloudy swelling of the retinal bipolar cells in acute thiamin deficiency. Triple × 1600.

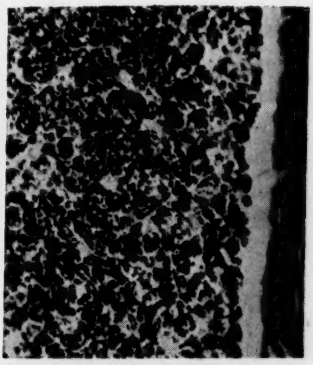

FIG. 3.—Gross destruction of myelin in main branch of sciatic nerve in acute thiamin deficiency. A portion of an unaffected twig can be seen on the right. Marchi × 140.

(4) As in Experiment 3, Recovered

Diet.—As in Experiment 3.

Clinical Behaviour.—Weights and heart rates are shown in Table III.

TABLE III

EXPERIMENT 4 (DURATION 60 DAYS)

Rat No.	Weights (g.)			Heart Rates (beats/min.)			Disposal
	Initial	At 15 days	Final	Initial	At 15 days	Final	
1	130	120	165	440	250	440	Killed
2	110	111	148	480	300	460	Killed
3	165	185	235	440	360	420	Killed
4	110	107	—	500	200	—	Died 13th day
5	120	115	155	480	240	480	Killed
6	135	121	—	460	—	—	Died

Rat 4 died on the 13th day. Rat 6 died suddenly during the recordings. The others were all spastic and inco-ordinated on the 15th day when their diet was restored. Rats 1 and 5 were given intraperitoneal thiamin as their heart rates were so low, and this was repeated for 3 days; otherwise they might not have lived. The four survivors (Rats 1, 2, 3, and 5) were killed on the 60th day.

Pathological Observations.—No signs of degeneration or repair in the visual pathway nor sciatic nerves were seen in the recovered rats.

(5) Reduced Thiamin Intake associated with High Carbohydrate Diet, inducing Chronic Deficiency

Diet.—

Stock (Glucose + W.S.V.)
Thiamin minimal ... ... as required

The adoption of a preconceived plan for the administration of thiamin to the group was rejected. We decided each animal required individual attention. A daily dose of 2 μg. was, therefore, administered individually until the first signs of anorexia. The dose was then increased in that rat to 5 μg. until the appetite returned, when 2 μg. was once again given, *ad infinitum*.

Clinical Behaviour.—As Table IV shows, Rats, 1, 3, and 4 existed quite happily on a daily maintenance dose of 2 μg., although they had gained on the average only about 18 g. in weight after 180 days. Up to the 12th week all the rats did well. The increase in weight was slow but steady. The animals were thin but fit, and their appetites had been maintained. Hereafter it was increasingly difficult to prevent anorexia in Rats 2, 5, and 6.

TABLE IV

EXPERIMENT 5 (DURATION 180 DAYS)

Rat No.	Weights (g.)			Heart Rates (beats/min.)			Disposal
	Initial	Final	Difference	Initial	Final	Difference	
1	95	100	+ 5	500	480	− 20	Killed on 180th day
2	90	90	0	500	360	−140	
3	90	120	+30	500	480	− 20	
4	92	110	+18	500	420	− 80	
5	90	95	+ 5	500	340	−160	
6	90	89	− 1	500	360	−140	

By the 160th day they had become bedraggled and shaky. There were no gross signs of inco-ordination, however, and they kept eating up to two-thirds of their daily ration. We observed a marked ptosis of the upper lids. Even when the animals were given a fright, the palpebral fissures remained reduced in size, and this appeared to be a true paralysis. The animals, moreover, appeared to be suffering from drop-foot, although this may have been due to fatigue. They still ate, however, and could sit up and wash

themselves. We observed one of them regurgitate while feeding on two occasions but vomitus was never seen. When the heart rates fell below 400 beats/min. (restrained), it was decided to end the experiment.

The continued good health of the other three rats was considered to be due to intestinal resynthesis.

Pathological Observations.—Rats, 1, 3, and 4 revealed no abnormality; Rats 2, 5, and 6 each exhibited identical changes.

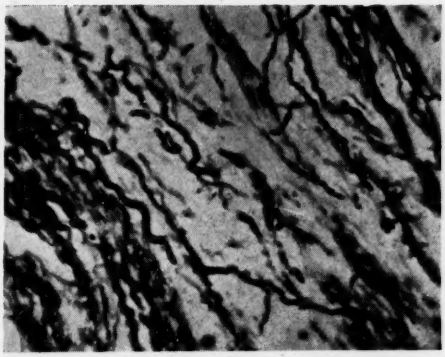

FIG. 4.—Fragmentation and tortuosity of optic-nerve terminals within dorsal nucleus in chronic thiamin deficiency. The larger fibres in the section are not fragmented. Author's silver × 670.

The retinal ganglion cells were hyperchromatic. That was the only change.

The optic nerve and tract revealed widespread signs of degeneration increasing in intensity as the fibres ascended: the nerve fibres were thickened, distorted, and very tortuous (corkscrew fibres). The terminal branches within the lateral geniculate body were similarly affected; and in addition the larger ones had fragmented (Fig. 4). There were many small black patches, which might have

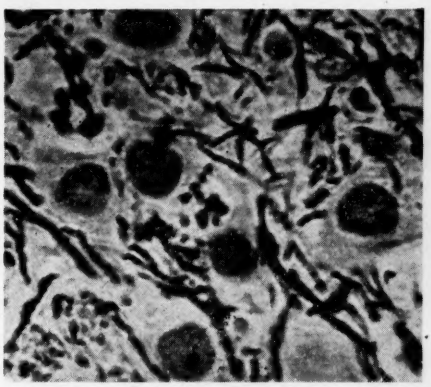

FIG. 5.—Enlargement of terminal nerve endings in chronic thiamin deficiency. Some argyrophil ring shapes are also present. Author's silver × 1000.

FIG. 6.—Final visual neurone within dorsal nucleus in chronic thiamin deficiency. Axon greatly swollen. Author's silver × 1000.

been distorted ring shapes. We found a few endings enlarged (Fig. 5). The fibres of the third neurone as far as we could see were varicose and thickened (Fig. 6).

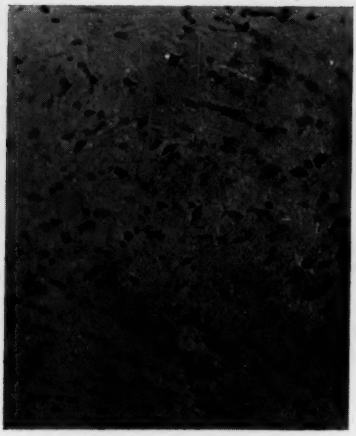

FIG. 7.—Sclerosis and hyperchromatism of visual neurones in chronic thiamin deficiency. Cf. Fig. 8. Giemsa × 175.

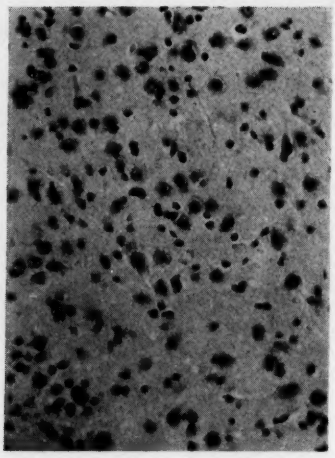

FIG. 8.—Unaffected visual neurones of dorsal nucleus in paired control animal. Giemsa × 175.

FIG. 9.—Aggregation of oligodendrocytes in chronic thiamin deficiency. Giemsa × 300.

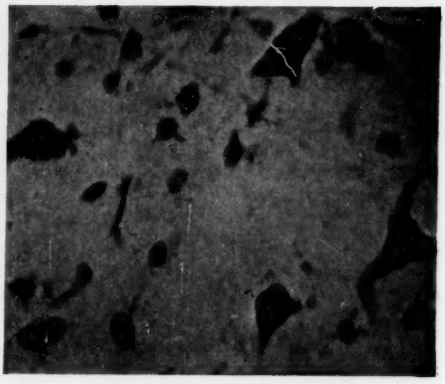

FIG. 10.—Sclerosis and hyperchromatism of visual neurones in chronic thiamin deficiency. Note presence of rod cells and cloudy swelling of astrocytes. Giemsa × 750.

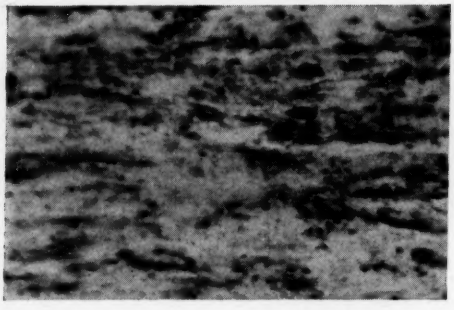

FIG. 11.—Fragmentation, globulation, and ballooning of persistent myelin sheaths in chronic thiamin deficiency. Weigert-Pal × 350.

Within the dorsal nucleus, the visual cells were nearly all hyperchromatic and sclerosed. The degree of sclerosis was not gross, but it was definite. Both nuclear and cellular outlines were distorted (Figs 7 and 8).

Within the optic nerve and tract, the oligodendrocytes had proliferated considerably into long chains (Fig. 9). These cells were of normal size, but the small amount of cytoplasm present was hyperchromatic. We did not find any evidence of satellitosis, but many rod cells were seen within the dorsal nucleus (Fig. 10).

These changes were widespread.

The myelin changes, although variable, were diffuse. In places the myelin had completely disappeared, many gitter cells being present. Where the myelin sheaths persisted, irregularity and ballooning was common (Fig. 11), and this was also true of some of the twigs of the sciatic nerves.

(5A) Paired Control

Diet.—As in Experiment 5.

Clinical Behaviour.—Table V shows the weights and heart rates of the six paired rats in Experiment 5A.

TABLE V

EXPERIMENT 5A, PAIRED CONTROLS (DURATION 180 DAYS)

Rat No.	Weights (g.)			Heart Rates (beats/min.)			Disposal
	Initial	Final	Difference	Initial	Final	Difference	
1A	100	265	+165	500	480	−20	Killed on 180th day
2A	90	180	+ 90	500	480	−20	
3A	102	275	+173	500	500	Nil	
4A	95	290	+195	500	460	−40	
5A	87	190	+103	500	460	−40	
6A	90	200	+110	500	480	−20	

These rats did well. Rats 2A, 5A, and 6A, being subjected to the vagaries of appetite in the paired experimental animals, were often hungry. Latterly all were hungry, 15 g. being evidently insufficient.

Pathological Observations.—No abnormality found.

(6) As in Experiment 5, Recovered

Diet.—As in Experiment 5.

Clinical Behaviour.—The weights and heart rates are shown in Table VI (overleaf). By the 63rd day, signs of deficiency were present. Rats 1, 3, 6, and 8 were moribund, intraperitoneal thiamin had no effect, and they died in convulsions. The others were shaky, but otherwise well, especially Rat 9, and heart rates were taken under light urethane.* Rat 5 did not

* This was only done if the rats were excitable when restrained by hand.

TABLE VI

EXPERIMENT 6 (DURATION 140 DAYS)

Rat No.	Weights (g.)			Heart Rates (beats/min.)		Disposal
	Initial	At 14th week	Final	Initial	At 14th week	
1	50	80	—	550	—	Died 63rd day
2	115	110	160	480	340	Killed 140th day
3	50	60	—	550	—	Died 63rd day
4	55	85	100	500	320	Killed 90th day
5	55	92	—	500	360	Died during recording
6	55	75	—	500	—	Died 63rd day
7	70	60	235	500	380	Killed 140th day
8	55	70	—	550	—	Died 63rd day
9	72	125	255	480	390	Killed 140th day

regain consciousness. Rat 2 was spastic next day, and all the survivors (including Rat 9, which was still very active) were given intraperitoneal thiamin, and a full diet was instituted. They made an uninterrupted recovery, gaining weight rapidly. Anorexia in this experiment had been remarkably well controlled so that the paired rats (Exp. 6A) seldom had to have their intake reduced. Rat 4 was killed on the 90th day, and the rest on the 140th. There was no residual palsy.

Pathological Observations.—Changes were found in Rats 2, 4, and 7. The visual path and eyeballs of Rat 9 were normal.

The changes in the retinae, which were not striking, consisted of the presence of what appeared to be " gemastëte cells ". These cells approached in size sclerosed ganglion cells, and might have been mistaken for them. The number of them present in 7μ. sections outside the macular region was, nevertheless, suggestive. The ganglion cells themselves were on the whole normal, although satellitosis around them was common. The other retinal elements were unaffected.

The visual cells in the dorsal geniculate nuclei were almost entirely normal; here and there a few were sclerosed, and there was widespread hyperchromatism of the glia, and some evidence of satellitosis (Figs 12 and 13). Many long oligodendrocyte chains were seen in the optic tract of Rat 2.

Changes in the nerve fibres were of an equally slight nature. A moderate degree of distortion appeared in the tract of Rat 2.

The nerves and tracts, however, revealed a high degree of patchy demyelinization, which was also present in the nerve head of Rat 7 (Fig. 14). None was found in Rat 4. Several hard grey plaques were found (Fig. 15).

The sciatic nerves showed circumferential degeneration involving some of the nerve trunks (Fig. 16). In others, there was distortion of the myelin sheaths when viewed transversely. Some sheaths exhibited ballooning.

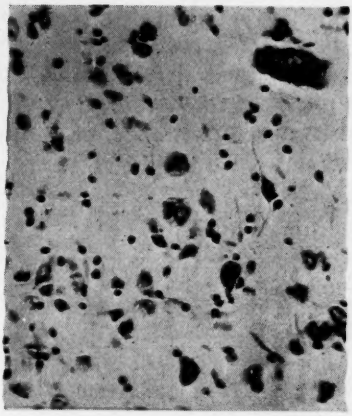

FIG. 12.—Hyperchromatic visual cell-bodies, hyperchromatism of glia, and slight evidence of satellitosis in chronic thiamin deficiency 57 days after recovery. Giemsa × 220.

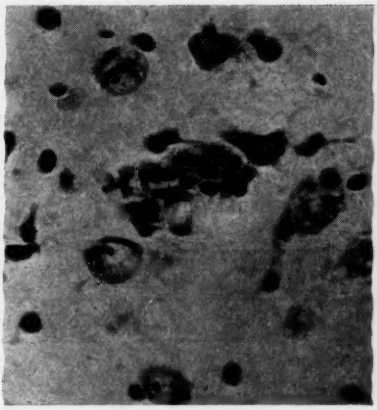

FIG. 13.—Satellitosis in recovered thiamin deficiency. Giemsa × 450.

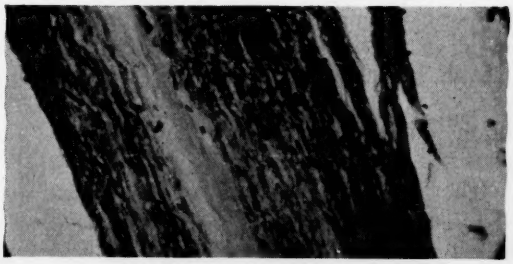

FIG. 14.—Central demyelinization of optic nerve in chronic thiamin deficiency. Loyez × 200.

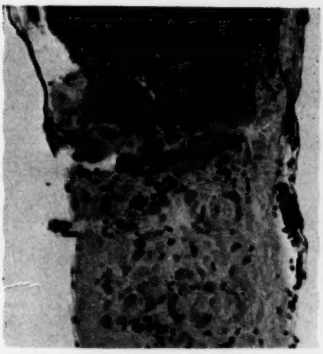

FIG. 15.—Hard grey plaque in optic tract in recovered chronic thiamin deficiency. Note clear delimitation of healthy sheaths above this region. Loyez × 150

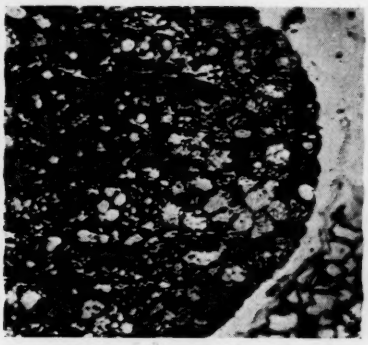

FIG. 16.—Persistent demyelinization of peripherally placed fibres in a large sciatic nerve twig in recovered chronic thiamin deficiency. Weigert-Pal × 140.

(6A) Paired Control

Diet.—As in Experiment 6.

Clinical Behaviour.—Weights and heart rates are shown in Table VII. As anorexia in the experimental rats had been well controlled, these rats flourished, seldom appearing hungry.

TABLE VII

EXPERIMENT 6A, PAIRED CONTROLS (DURATION 140 DAYS)

Rat No.	Weights (g.)		Heart Rates (beats/min.)		Disposal
	Initial	Final	Initial	Final	
2A	110	220	480	440	Killed on 140th day
4A	55	190	500	480	
7A	60	188	500	480	
9A	68	200	500	460	

Pathological Observations.—No abnormality found.

Discussion

The results of these experiments show that optic and sciatic nerve atrophy can be produced in rats fed a diet high in carbohydrate at a level of thiamin inadequate for health, but sufficient to keep the animals alive over a period of about 180 days.

The degeneration found in the visual pathways of rats fed under such circumstances consisted of a slight degree of hyperchromatism and sclerosis of the retinal ganglion cells, and in more marked degree of the cells in the dorsal nucleus of the lateral geniculate body. In addition there was a striking proliferation within the optic nerve and tract of oligodendrocytes which formed long interfascicular chains; rod cells were present in great abundance in the dorsal nucleus; and here and there in the same region neuroglial hyperchromatism. The most important sign of all was the tortuosity, varicosity, and fragmentation of the visual fibres, especially of their central terminations. Enlargement of synaptic *boutons* and an increase in argyrophil ring shapes were also seen. The myelin sheaths in their turn exhibited a patchy demyelinization, several soft plaques were observed, and, in many of the persistent sheaths, irregularity of outline and ballooning.

These changes, indicative of severe neuronal degeneration, were found to be reversible with the following exceptions. The proliferation of the glia persisted 76 days after re-institution of a full diet, as did the glial hyperchromatism; the nerve fibres remained more tortuous than in the paired animals; the myelin lesions were for the greater part unchanged. A new feature in the recovered animals was the appearance of several hard grey plaques.

The paired control rats in the chronic thiamin deficiency experiment,

having a high intake of thiamin, never presented this picture. They were under close observation throughout; their behaviour remained perfectly normal, and their appetites were excellent, although at times they went hungry. Subsequently, as has been said, the visual pathways revealed no abnormality whatsoever. It seems certain, then, that the histological changes in the central and peripheral nervous systems described above arose as a result of thiamin deficiency, and for no other reason. At any rate, anorexia had never been gross or prolonged in the deficient animals. The cell bodies within the central nervous system were distorted in those rats which were made to die of inanition at the end of 18 days, but the peripheral processes were never affected. This, it is believed, is a highly significant observation, yet, in the paired controls, not even this change was found.

The changes found in the sciatic nerves in chronic thiamin deficiency were striking, but should be stressed again that they were not examined in every case, nor was every twig sectioned in those nerves chosen. It is certain, however, that here as in the optic nerve demyelinization of a gross nature resulted. The interesting feature is that the degenerative process appeared to affect some twigs and not others in the same nerve, and that it was the peripheral fibres in a twig which were affected first. This perhaps explains the discrepancies expressed in the literature. These myelin changes were for the greater part irreversible. For the same reasons as are given above, inanition could not be responsible.

In acute thiamin deficiency, inanition was gross in the last day or two of life, yet the visual pathway was not affected other than by a slight cloudy swelling of the retinal bipolars. There was no fragmentation nor demyelinization of the visual fibres, nor was there sclerosis of the geniculate neurones. The marked demyelinization found in the sciatic nerves may have been due to this terminal inanition, but the evidence does not altogether support this view. In the two 'inanition' experiments, the sciatic nerve changes were not marked. Under the polarizing microscope, there was some granular isotropism of the myelin, but no more than that. Nevertheless, since the rats used were older, one hesitates to be dogmatic in claiming that acute thiamin deficiency leads to sciatic nerve atrophy, though it certainly appears to accentuate it, in the presence of inanition.

It was interesting to find that in acute deficiency, the gross myelin changes found in the sciatic nerves were recoverable, whereas in chronic deficiency, the less gross changes were not recoverable. It is possible that the degree of myelin-recovery depends upon the integrity of the nerve cells and their processes, for in acute deficiency (by analogy with the state of the visual neurones) the latter were intact, whereas in the chronic condition there were always residual signs of cell-body disease. On these grounds it seems probable that as a general rule the integrity of myelin depends upon the integrity of the cell-body, although the reverse is obviously not true. This belief has been expressed by several workers in the past.

To return to the visual neurones, just as different rats appear to be more susceptible, so some fibres seem to be more readily affected than others. As we do not know the pathway taken by the macular fibres in the rat, however, we could not say, even if only the central fibres *had* degenerated, that the papillo-macular bundle was more susceptible than any other.

It is important to note that the lesions produced in myelin by a thiamin deficiency of long duration were *disseminated* throughout the visual pathway, and increased in severity as they ascended. This fact lends support to our belief that the retinal ganglion cells are not greatly affected, a somewhat paradoxical finding in view of their extremely low resistance to chemical poisons, and the generally held opinion that the causative agent in thiamin deficiency is an endogenous toxin, specifically affecting the macula.

The appearance of the retina in the chronic experiments, however, suggests that, if the thiamin deficiency had been even more prolonged, the retinal ganglion cells would have become just as much affected in the end as were the visual cells of the diencephalon. Perhaps the explanation of the long retinal immunity is to be found in the extremely active drainage afforded by the choriocapillaris.

Changes affecting the retinal pigment or the blood vessels were not found in any specimen. Furthermore, there was a total lack within the visual path of any sign of a haemorrhagic crisis, although the Giemsa technique is particularly suited for such observations. Although the floor of the IVth ventricle was not investigated and this is the preferential site for such haemorrhages in the rat, we seem to have been justified in leaving the rat to manufacture its own vitamin K.

The endogenous supply of vitamin C was also adequate for there were no signs of scurvy.

Summary

(1) When thiamin deficiency in rats is of moderate degree and prolonged for about 180 days or over, degeneration of the visual pathway develops in certain susceptible animals, its intensity being greatest centrally. This occurs even when the caloric intake is adequate.

(2) A chronic degeneration of this type comprises three distinctive features:

(*a*) The visual cells become sclerosed and hyperchromatic, the retinal much later than the geniculate.

(*b*) The axis cylinders become thickened, tortuous, and varicose, the terminal branches fragmented, and the nerve endings enlarged. Ring shapes increase.

(*c*) Multiple foci of demyelinization occur, to be replaced in time by clearly delimited glial plaques.

(*d*) Long chains of oligodendrocytes form, and rod cells appear in the lateral geniculate body.

(3) The chronic deficiency is also associated with demyelinization of some of the twigs of the sciatic nerves, affecting particularly the peripheral fibres.

(4) These changes are reversible only when the cell-body and its process has not been unduly damaged. Myelin-sheath recovery is probably dependent upon complete recovery of the soma.

(5) In acute thiamin deficiency, the visual pathway is not affected, but the sciatic nerves become grossly demyelinated. This demyelinization is completely reversible. It is probably associated with inanition.

(6) Demyelinization of the sciatic nerves also occurs in rats fed a diet totally inadequate in calories with or without vitamins, but in this case is much less gross than when combined with acute thiamin deficiency.

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REFERENCES

ARNOLD, A., and ELVEHJEM, C. A. (1938). *J. Nutr.*, **15**, 403.
BARLETTA, V. (1932). *Rass. ital. Ottal.*, **1**, 210.
BERRY, C., NEUMANN, C., and HINSEY, J. C. (1945). *J. Neurophysiol.*, **8**, 315.
BEST, C. H., and TAYLOR, N. B. (1950). " The Physiological Basis of Medical Practice ", 5th ed. Baillière, Tindall and Cox, London.
COWARD, K. H. (1947). " The Biological Standardisation of the Vitamins ", 2nd ed. Baillière, Tindall and Cox, London.
DAVISON, C., and STONE, L. (1937). *Arch. Path., Chicago*, **23**, 207.
DRUMMOND, J. C., and MARRIAN, G. F. (1926). *Biochem. J.*, **20**, 1229.
DRURY, A. N., HARRIS, L. J., and MAUDSLEY, C. (1930). *Ibid.*, **24**, 1632.
ENGEL, R. W., and PHILLIPS, P. H. (1938). *J. Nutr.*, **16**, 585.
FERRARO, A., and ROIZIN, L. (1943). *J. Neuropath.*, **2**, 392.
FOLLIS, R. H., MILLER, M. H., WINTROBE, M. M., and STEIN, H. J. (1943). *Amer. J. Path.*, **19**, 341.
LEINFELDER, P. J., and ROBBIE, W. A. (1947). *Amer. J. Ophthal.*, **30**, 1135.
MCDERMOTT, W., WEBSTER, B., BAKER, R., LOCKHART, J., and TOMPSETT, R. (1943). *J. Pharmacol.*, **77**, 24.
MARCHESINI, E., and PAPAGNO, M. (1935). *Ann. Ottal.*, **63**, 81.
PETERS, R. A. (1934). *Proc. roy. Soc. Med.*, **27**, 478.
PRADOS, M., and SWANK, R. L. (1942). *Arch. Neurol. Psychiat.*, **47**, 626.
PRICKETT, C. O. (1934). *Amer. J. Physiol.*, **107**, 459.
——— SALMON, W. D., and SCHRADER, G. A. (1939). *Amer. J. Path.*, **15**, 251.
RODGER, F. C. (1951). " The Relationship of Thiamin to the Visual Pathway ". Thesis. Glasgow University.
SHAW, J. H., and PHILLIPS, P. H. (1945). *J. Nutr.*, **29**, 113.
SWANK, R. L., and BESSEY, O. A. (1941). *Ibid.*, **22**, 77.
——— and PRADOS, M. (1942). *Arch. Neurol. Psychiat., Chicago*, **47**, 97.
WINTROBE, M. M., FOLLIS, R. H., HUMPHREYS, S., STEIN, H., and LAURITSEN, M. (1944). *J. Nutr.*, **28**, 283.
WOOLLEY, D. W., and WHITE, A. G. C. (1943). *J. biol. Chem.*, **149**, 285.
YUDKIN, J. (1951). *Biochem. J.*, **48**, 608.
ZIMMERMAN, H. M. (1943). *Res. Publ. Ass. nerv. ment. Dis.*, **22**, 51 and 75.

Brit. J. Ophthal. (1953) **37**, 30.

CONTROL OF EXPERIMENTAL CORNEAL INFECTION WITH MEDICATED SEMI-SOLID CONTACT CAP AND DISK*

INFECTION WITH *Ps. PYOCYANEA* TREATED WITH STREPTOMYCIN

BY

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London

MULES (1894) wrote that where " the action of micro-organisms on an abraded surface may cause or is causing destructive changes " the indications would be to remove the irritating elements and allow the natural process of repair to heal the breach of surface ". He sought to achieve this by placing a gelatine wafer impregnated with iodoform on the corneal surface and keeping the eye bandaged. He reported twelve cases in all of which healing was spectacular.

Adam (1916) used a contact shell made of glycerin gelatine for the protection of the globe in cases of injuries around the orbit, and Huber (1934) used a contact shell carrying iodoform-cocaine-dionine ointment for the treatment of hypopyon ulcer.

The treatment of corneal ulcers, especially those caused by Gram-negative micro-organisms, is not satisfactory. In a series of ten corneal ulcers caused by *Ps. pyocyanea* infection reported by Bignell (1951), the eye had to be eviscerated in four cases, in three cases the residual vision was perception of light only, and in the remaining three the vision was 6/18, 6/24, and 6/36 respectively. The disastrous effect of this type of infection is emphasized when it is appreciated that treatment in this series started between two and four days after injury (usually a corneal foreign body) and consisted of the newer antibiotics, including aureomycin and streptomycin. Those cases which did better received streptomycin subconjunctivally, usually in conjunction with other treatment, either sulphonamide or local aureomycin.

Various cases have been reported in which local streptomycin has proved of value in severe corneal ulcers. Thus Couadau and Darbon (1948) used this antibiotic in a case of keratitis due to *B. faecalis alcaligenes*, Clark and Locatcher-Khorazo (1951) in corneal ulcer produced by *B. aerobacter aerogenes*, Maschler (1948) in a *Ps. pyocyanea* ring abscess, Lepri (1948) in a post-traumatic corneal infection by *Proteus Morgani*, and Sorsby, Ungar and Bailey (1952) in nine cases of corneal ulcers, two of these being caused by *Ps. pyocyanea* treated with streptomycin.

The problem of pyocyanea infections of the cornea was investigated in rabbit experiments by Grün and Reinhart (1949), who used subconjunctival injections of streptomycin, starting treatment on the second day after infection when the corneal ulcer was established. They came to the conclusion that streptomycin alone is not sufficient to cause healing, but

* Received for publication July 21, 1952.

that when it was supplemented with oral or local administration of sulphonamide the ulcers healed. Apparently they did not add adrenaline to the solution used for subconjunctival injection.

Recently Sorsby, Ungar, and Bailey (1952), in a series of rabbits, successfully prevented the *Ps. pyocyanea* infection by subconjunctival injections of 0.5 g. dihydro streptomycin dissolved in liq. adrenaline, 3 hrs after infection.

Present Investigations

We have aimed at ascertaining whether a semi-solid alginate cap or gelatine disk carrying the antibiotic or drug would ensure a more prolonged action than that obtainable by instillation of drops or by the use of ointments.

Experimental Technique.—Infection of the cornea was produced in the anaesthetized rabbit's eye mostly by intracorneal injection of a suspension of 24-hour-old broth culture of a freshly subcultured human pathogenic *Ps. pyocyanea*. A small wheal of about 4 mm. diameter was produced by the fluid injected into the superficial layers of the cornea. Next day in the untreated eyes an ulceration with dirty grey base was present, which led eventually to extensive scarring and shrinkage of the globe or to ectatic cornea. In a few experiments the infection was produced by scarifying an area of 4 sq. mm., placing one drop of the pyocyanea suspension over the area and rubbing it in with the scarification needle. Treatment, which was given immediately, consisted of:

(*a*) subconjunctival injection of streptomycin,
(*b*) streptomycin powder applied in an alginate cap,
(*c*) gelatine disk containing 20 per cent. streptomycin,
(*d*) glycerine gelatine disk containing 20 per cent. streptomycin.

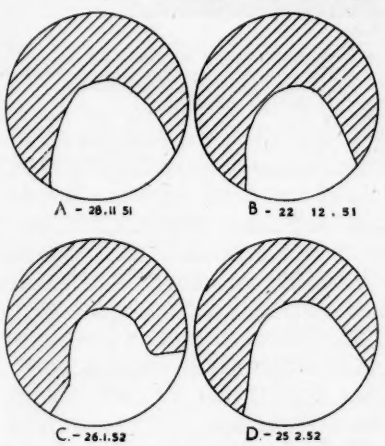

FIG. 1.—Area of inhibition (shaded) remained almost the same. The disks were made on November 5, 1951.
(A) Plate test November 28, 1951.
(B) December 22, 1951.
(C) January 26, 1952.
(D) February 25, 1952.

The alginate cap or gelatine disk was kept in the conjunctival sac by closing the lids with a single central suture. The gelatine or glycerine gelatine disks used in the majority of these experiments, were made as follows:

A Perspex plate containing drill holes ½″ (12 mm.) in diameter rested on a sheet of Perspex or glass, and the streptomycin gelatine solution was poured into the drill holes. After they had set, the disks were removed and stored in a wide-mouthed jar.

The gelatine-lamella-base disks proved unsuitable because if kept in an uncovered jar they dried out and became brittle, and if kept in a well-closed container they retained their consistency, but were liable to bacterial and fungus contamination. The glycerine gelatine disks kept for 4 months in a jar, showed no contamina-

tion with moulds, and remained the same when the area of inhibition for *Ps. pyocyanea* was tested by the plate method (Fig. 1). These tests were made after completion of the experiments, and the stored disks were not assayed in experimental infection.

Results

Table I shows that 0.5 g. streptomycin (in 1 ml. 0.5 per cent. amethocaine solution with 2 min. adrenaline 1: 1,000) given as a single sub-

TABLE I

TREATMENT WITH STREPTOMYCIN SUBCONJUNCTIVALLY

Rabbit No.	Mode of Infection	Treatment	Result after 24 hrs	Remarks
1	Intracorneal injection, *Ps. pyocyanea*	0.5 g. subconjunct. c. adrenaline	Clear	Remained clear
2		,, ,,	Moderate infection	Became worse
3		,, ,,	Clear	Remained clear
4		,, ,,	Clear	Remained clear
5		Control	Heavily infected	
6		Control	Heavily infected	

TABLE II

TREATMENT WITH STREPTOMYCIN ADMINISTERED IN CALCIUM ALGINATE CAPS OR GELATINE OR GLYCERINE-GELATINE DISKS

Rabbit No.	Mode of Infection	Treatment	Result after 24 hrs	Remarks
1	Intracorneal injection *Ps. pyocyanea*	60 mg. in calcium alginate cap	Clear	Remained clear
2		,, ,,	Clear	Remained clear
3		0.1 g. in gelatine disk	Clear	Remained clear
4		,, ,,	Infected	The eyes were found open and it is suspected that the rabbits scratched off the lid suture and the gelatine came out too soon
5		,, ,,	Infected	
6		,, ,,	Clear	Remained clear
7		,, ,,	Clear	Remained clear
8		,, ,,	Clear	Remained clear
9		21-day-old gelatine disk	Infected	Progressively worse
10	Scarification of cornea 1 drop 24-hr culture rubbed in	0.1 g. in glycerine-gelatine disk	Clear	Remained clear
11		,, ,,	Clear	
12		,, ,,	Clear	
13		,, ,,	Clear	
14	Intracorneal injection	Control	Heavy infection	
15		Control		
16		Control		
17	Corneal scarification plus 1 drop culture	Control		
18		Control		

conjunctival injection protects the cornea. The infection employed was a massive one such as does not occur in clinical practice, yet in three out of four eyes the cornea remained clear.

In the experiments tabulated in Table II the streptomycin was administered by alginate cap or in gelatine or glycerine gelatine disks. It is seen that in an alginate cap as little as a single dose of 0.06 g. streptomycin is capable of preventing the development of the corneal infection, while in gelatine or glycerine gelatine disks 0.1 g. gave protection against massive infection (Figs 2 and 3). From experiments with chloramphenicol (Klein and Millwood,

FIG. 2.—Untreated eye 3 days after infection with *Ps. pyocyanea.*

FIG. 3.—Protective effect of streptomycin glycerine-gelatine lamella. Infection completely controlled.

1952) it was known that the rabbit eyes do not take kindly to calcium alginate shells, and for this reason we searched for another method. The gelatine disks were well tolerated, but it was found however that at body temperature they melted and if freshly made quickly disappeared from the conjunctival sac. If however the disks were stored for longer than a week (*vide supra*) they were liable to become contaminated with fungi and lose potency, or to dry out and cause injury to the eye. In one experiment (No. 9, Table II) where a 21-day-old gelatine disk was used, the cornea became infected. However, glycerine gelatine disks (suggested by Mr. Frank Allen) have a much longer shelf life [they do not dry out even if left in an uncovered jar, and no contamination with moulds has so far been noticed] and have marked protective action (Nos 10, 11, 12, 13, Table II).

When the streptomycin-calcium-alginate cap was removed from the eye after 24 hours, and cultured, no growth of *Ps. pyocyanea* was found although other organisms were present. Streptomycin is bacteriocidal, and employed in a suitable form comes near to Mules's requirement " to remove the

irritating element, and then the natural process of repair will heal the breach of surface ".

In order to compare the effectiveness of the medication in caps or disks with the subconjunctival method the same amount of streptomycin as was effective by the disk method was injected subconjunctivally. As Table III shows no protection was afforded to the cornea.

TABLE III

TREATMENT WITH SMALLER DOSES OF STREPTOMYCIN SUBCONJUNCTIVALLY

Rabbit No.	Mode of Infection	Treatment	Result after 24 hrs	Remarks
1	Intracorneal injection *Ps. pyocyanea*	30 mg. in sod. alginate	Heavy infection	Progressively worse
2		60 mg. in sod. alginate		
3		60 mg. c. adrenaline		
4		60 mg. c. adrenaline		
5		Control		
6		Control		

It seems that, in these series of experiments, 0.5 g. given subconjunctivally compares with 0.06 g. administered in an alginate cap and 0.1 g. administered in disk form.

Discussion

Atypical corneal ulcers, corneal abscesses, and proteolytic ulcers (Sorsby and others, 1952) are mostly caused by Gram-negative organisms, and many of them by *Ps. pyocyanea*. The infection is often preceded by the presence of a foreign body in the eye which has been removed, or by some trivial injury. They do not respond to routine treatment, and are usually resistant to penicillin, and in spite of treatment the neighbouring clear corneal portions become invaded with such rapidity that in a few days almost the whole cornea may be destroyed. Until recently these infections were regarded as almost certain losses. Lately, however, sporadic successes with streptomycin have been published.

With systemic administration of streptomycin the concentration reached in the ocular tissues is very poor (Leopold, 1950) and in the case of the cornea there is the added disadvantage that its circulation, especially in the central parts where many of these ulcers occur, is very slow. Streptomycin administered systemically is therefore ineffective. Experiments have shown that the large molecule of streptomycin penetrates the intact corneal epithelium poorly if administered locally in eyedrops, or ointment, and only slightly better by iontophoresis. When the epithelium is abraded the penetration is considerably increased and one would therefore expect local treatment to be effective in corneal ulcers. In the series of cases reported

by Bignell (1951) those treated by streptomycin eyedrops were failures, probably because the concentration in the tissues was not continuously maintained. It is known (Ridley, 1931) that eyedrops disappear from the conjunctival *cul de sac* in a matter of minutes. With this form of treatment therefore an optimum concentration for an adequate time is not obtainable.

With ointments the drug is embedded in the ointment base, and release from the vehicle is uncertain; especially in a water-in-oil type of ointment, or if the drug is suspended in a greasy vehicle without a solvent. With subconjunctival injections rapid improvements were achieved (Bignell's Cases 4, 8, 10, 1951; Clark and Locatcher-Khorazo, 1951; Sorsby and others,1952).

In the experiments here presented streptomycin was administered locally in a calcium alginate cap, or in a gelatine or glycerine gelatine disk. This method of administration seems to be effective against experimental ocular infection with *Ps. pyocyanea.*

It is significant that one-fifth of the effective dose of streptomycin administered subconjunctivally was sufficient to control the infection when given by this method. If the same amount of streptomycin was used subconjunctivally which was effective with the glycerine-gelatine disk the former was ineffective. The present investigation supports the results of Sorsby and others (1952) and it is suggested that with subconjunctival injection a minimum dose of 0.5 g. streptomycin with added adrenaline should be regarded as the standard treatment for pyocyanea infection of the cornea.

Clinically there are two distinct problems, that of prevention, and that of treatment. For prevention it seems reasonable that in the first-aid posts of factories where most of these infections seem to occur, after removal of a foreign body or treatment of a superficial corneal lesion, streptomycin should be inserted into the conjunctival sac. The form of application to be used will be decided in the light of experience, and it is possible that a single application of a streptomycin ointment may be sufficient. Better still, a glycerine-gelatine-streptomycin disk with a content of 0.1 g. streptomycin should be placed in the *cul de sac* and the eye bandaged. In any case some form of streptomycin, suitable for the local treatment of the eye, should be kept in the medicine chest of the first-aid post. The glycerine-gelatine disks proved successful in laboratory experiments but their tolerance by the human eye needs further investigation. The disks should be stored in a refrigerator, and replaced every 3 months because in the presence of the small amount of water in the disks the streptomycin content may diminish.

For the treatment of an established infection with *Ps. pyocyanea* the standard method of subconjunctival streptomycin is recommended. If, however, for any reason the subconjunctival injections cannot be given, as for instance in cases of painful reaction to injection, streptomycin in glycerine-gelatine disk 3 times a day is the next choice. The eye must be kept bandaged to keep the disk in place after insertion. The experimental findings justify an extended clinical trial of this procedure.

Summary

A single application of 0.1 g. streptomycin in the form of a glycerine-gelatine disk was able to control a massive corneal infection with *Ps. pyocyanea* in rabbits.

It is suggested that streptomycin locally applied should be used as a routine prophylactic in cases of superficial injuries of the eye in industrial first-aid posts, and that streptomycin ointment or disks should be kept in store in the medicine chest.

For the treatment of a corneal ulcer due to infection with *Ps. pyocyanea* the established treatment of subconjunctival injection of a minimum dose of 0.5 g. streptomycin with added adrenaline is recommended, and glycerine-gelatine-streptomycin disks may be used as a supplement.

In cases of intolerance to subconjunctival administration the glycerine-gelatine-streptomycin disks are worth trying.

Our thanks are due to Dr. W. W. Walther for permission and facilities to carry out the experiments in the Area Laboratory, Whipps Cross Hospital, London, and to Mr. Frank Allen, Chief Pharmacist, Whipps Cross Hospital, for his co-operation.

REFERENCES

ADAM, . (1916). *Z. Augenheilk.*, **36**, 100.
BIGNELL, J. L. (1951). *British Journal of Ophthalmology*, **35**, 419.
CLARK, G., and LOCATCHER-KHORAZO, D. (1951). *Arch. Ophthal., Chicago*, **45**, 164.
COUADAU, ., and DARBON, A. (1948). *Bull. Soc. d'Ophtal., Paris*, p. 815.
GRÜN, P., and REINHART, W. (1949). *Klin. Mbl. Augenheilk.*, **115**, 390.
HUBER, E. (1934). *Arch. Oftal. B. Aires*, **9**, 317.
KLEIN, M., and MILLWOOD, E. G. (1952). *British Journal of Ophthalmology*, **36**, 679.
LEPRI, G. (1948). *Arch. Ottal.*, **52**, 231.
——— (1948). Abstr. No. 2630. *Ophthal. Lit., Lond.*, **2**, 262.
MASCHLER, J. (1948). *British Journal of Ophthalmology*, **32**, 426.
MULES, B. (1894). Trans. VIII internat. ophthal. Congress, Edinburgh, p. 60.
RIDLEY, F. (1931). *Proc. roy. Soc. Med.*, **25**, 480.
SORSBY, A., UNGAR, J., and BAILEY, N. L. (1952). *Brit. med. J.*, **1**, 119.

Brit. J. Ophthal. (1953), **37**, 37.

SUPPRESSION THEORY OF BINOCULAR VISION*

BY

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THE problem of how an object may be perceived as single when it is viewed with both eyes is one which is not yet solved. In the past, du Tour (1760) and other scientists found that there was no fusion of the two images, but that always one of a pair of corresponding points suppressed the other. Another view was that of Heine (1900), who held that there was a single common centre which could be stimulated simultaneously by pathways originating from the two retinae. A third view is that of Sherrington (1906), who held that a single sensation arose from the fusion of two sensations which originated separately, one from each visual pathway.

Du Tour's theory was put forward before there was any knowledge of depth perception due to disparity of the retinal images. It was considered by both Wheatstone (1838) and Panum (1858), but was thought to be incompatible with data from experiments with stereoscopes, and not to fit in with the idea of disparity as a clue to depth perception. It is proposed here to reconsider du Tour's opinion in relation to the problem of depth perception.

Method of Viewing the Diagrams.—The diagrams shown in this paper should be combined as in a stereoscope. The most convenient way to do this is as follows:

The observer places his elbows and the diagrams on the table, holds in each hand a 3-dioptre convex lens which he places close up to his eyes, and views through their inner halves the two diagrams to be combined. Sideways adjustment of the lens position will aid combination. Since the images will be near infinity, the accommodation should be relaxed and the normal distance spectacle correction, if any, should be worn.

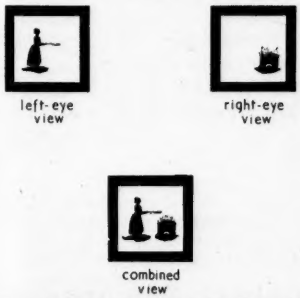

FIG. 1.—Experiment 1 (after Panum, 1858). The black of both lady and stove completely suppresses the corresponding portion of white ground seen by the other eye. (The lady may run into the fire; to move her out, fixate a vertical edge of the frame).

Experiments

Experiment 1 (Fig. 1).—The left eye views the lady, the right eye views the fire, and in the combined picture the lady is seen cooking over the fire. The black frame is seen by both eyes. Although the lady and the fire are each seen by one eye only, they appear equally as black as the frame which is seen by both eyes. Thus the portions of white ground corresponding to the lady and the fire are completely inhibited.

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Experiment 2 (Fig. 2).—The two pictures show left-eye and right-eye views of a small model archway. Notice that the right eye can see through the archway but the left eye cannot. When the two pictures are combined, the depth effect emerges. Also the appearance of the archway will be either that of the right-eye view or that of the left-eye view. The scene will not appear as a mixture of the two views, although the two may alternate. Thus one bit of archway always suppresses the other.

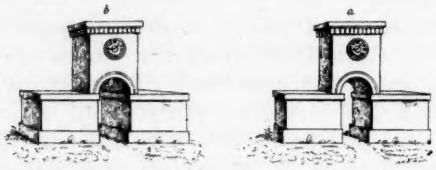


FIG. 2.—Experiment 2 (after Wheatstone, 1838). Shows the suppression which occurs with disparity of the retinal images. The appearance of the archway indicates which eye is dominant for this part of the picture.

Experiment 3 (Fig. 3, Wheatstone's cross).—Left-eye and right-eye views are shown of a cross consisting of a thin vertical bar and a thick horizontal bar. The cross is in front of the observer, below the level of his eyes, and so placed that the horizontal member lies in the vertical plane containing the right visual axis. A dot is placed above the line in the right-hand picture. When the top of each vertical line is fixated, the combined appearance shows the following features:

(1) A vivid depth effect with the thick horizontal bar apparently passing through the paper.
(2) A vertical line which may be thin, or thick, or may alternate between thick and thin.
(3) A dot which always appears above the vertical line.

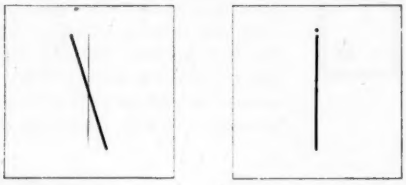


FIG. 3.—Experiment 3 (Wheatstone's cross, 1838).

Experiment 4 (Fig. 4*a*, *b*, and *c*).—To combine the diagrams of Fig. 4(*a*) each eye should fixate the disk. The line and the square then fall on disparate areas and appear to be well separated from each other.

In Fig. 4(*b*), when each eye fixates the lower disk, then the upper disks fall on disparate areas. Now a single upper disk is seen to be displaced apparently towards the observer.

In Fig. 4(*c*) the lower disks are again fixated, and as in Fig. 4(*b*) a single upper disk is seen to be displaced apparently towards the observer. In the combined view, the dot appears in the same position in relation to the lower disk as in the right-hand diagram.

FIG. 4.—Experiment 4.
(*a*) When the disks are fixated, the square and the line appear to be separated because they do not fall on corresponding points.

(*b*) When the two lower disks are fixated, the upper disks fall on disparate areas, but they are nevertheless seen as single.

(*c*) The lower disks are fixated, and a single upper disk is seen. The position of the dot in the combined view is the same as in the right-eye view, The correspondence of elements in this region has not changed.

Experiment 5 (Fig. 5).—When these two diagrams are combined the disks appear disposed in depth as before. If the upper disks are fixated then in the mental picture the single upper disk has a cross above and below it with a dot to the right. If the eyes are now moved down to fixate the lower disk, the crosses take up the position illustrated in the combined view, and appear to be in line with the dot.

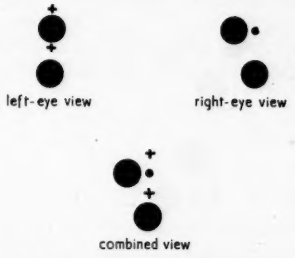


FIG. 5.—Experiment 5. The eyes fixate first the upper disks, then the lower ones. The movement of the crosses is immediately apparent, and is such as to show that correspondence is maintained. The left upper disk may or may not appear in the combined view.

Experiment 6 (Fig. 6).—The eyes are directed so as to cause the centre of the left upper disk to fall on the fixation point of the left eye, while the small dot falls on the fixation point of the right eye. An experienced observer can achieve this without difficulty, and when this position is attained it is easily maintained because the lower disks now fall on corresponding points, so that the eyes are to some extent locked in this position. The appearance is now as shown in the figure. The black dot is distinguished from the black disk on which it is superimposed because it carries with it some of its own white surround. The gaze is now directed downwards to fixate the apparently single lower disk. This is very easily done by a simple downward movement of both eyes without any change in convergence. The mental picture now changes to that shown in Fig. 6; the disk which before surrounded the dot is seen to disappear from it, and the dot itself does not move.

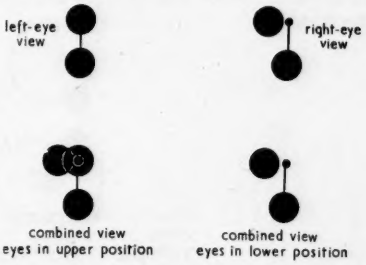


FIG. 6.—Experiment 6. The left eye fixates the upper disk and the right eye fixates the dot. Both upper disks are seen, that from the left eye appearing to be superimposed upon the dot.
The eyes now move down to fixate the lower disks, whereupon the upper disk seen by the left eye fades out. There is no lateral movement of this disk.

It is very instructive to repeat this experiment with a slow downward movement of the eyes, when the disk will be seen to fade away gradually. When careful attention is paid

to the presence of this disk it can be dimly perceived even in the lowermost eye position when the lower disks are fixated.

It is very clearly observed that the disk fades out slowly, and the emergence of the vivid stereoscopic appearance is likewise quite unmistakable. The precise time relation between these two processes is not easy to observe, but it would seem that the stereoscopic appearance is well established before the disk on the dot has faded out.

Experiment 7 (Fig. 7).—The small dot is transferred to the left-hand picture. The left eye now fixates the dot, and the right eye fixates the upper disk; this brings the lower disks onto corresponding points and maintains the position stable. The appearance is as shown in the Figure. On transferring the gaze to the apparently single lower dot, the eyes execute a conjugate movement downwards and to the right without any change of convergence. The appearance may now be either that of (*a*) " left eye dominant " or that of (*b*) " right eye dominant ". These are flat views of a three-dimensional mental picture; in each case the upper disk appears to be the nearer of the two.

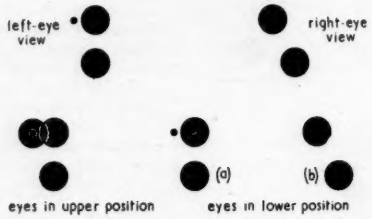


FIG. 7.—Experiment 7. The left eye fixates the dot and the right eye fixates the upper disk. The upper disks now fall on disparate areas and are seen as double.
The eyes now move down to fixate the lower disks. The upper disks continue to fall on disparate areas, but now they may be seen as single. Either of these two appearances is possible according to the dominance of the left or right eye: (*a*) shows left eye dominant, (*b*) shows right eye dominant.

Experiment 8 (Fig. 8).—The two pictures shown in the Figure represent the left-eye and right-eye views of three spheres arranged in a vertical plane containing the left visual axis. Of the two top spheres the left eye can see only the near one which hides the hinder one from view. When the pictures are combined the three-dimensional scene is vividly reproduced.

FIG. 8.—Experiment 8. The eyes fixate the bottom disks. Two upper disks are perceived, one nearer and one further away than the bottom disk. To account for this by the fusion theory, the upper disk of the left eye would have to change its correspondence in two different directions simultaneously.

Experiment 9 (Fig. 9).—This is similar in essentials to Experiment 8, but many observers find it easier to perform and more striking.

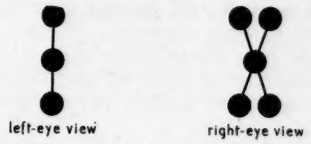


FIG. 9.—Experiment 9.

Experiment 10 (Fig. 10)

Part 1.—Each eye fixates the top of the left line of the pair. In the combined picture the apparent separation of the lines may be either that of the pair seen by the left eye or that of the pair seen by the right eye. These two appearances may alternate.

Part 2 (*Panum's experiment*).—The ground of the left card is made red and that of the right card is made blue. It is observed that the space between the vertical lines may be seen in various ways:

> partly blue and partly red; blue; red; both blue and red simultaneously as if one were perceived through the other.

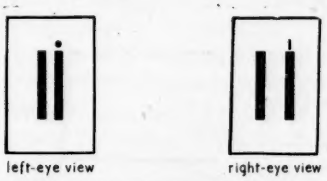


FIG. 10.—Experiment 10 (after Panum, 1858). The right line may be suppressed either by the left or by the right eye. The dot and the small line are subsidiary marks to indicate which line is seen and which is suppressed.

Experiment 11 (Fig. 11).—Left-eye and right-eye views of a black disk are seen through a hoop. Two subsidiary marks are provided to ensure accurate fixation. With fixation steadily maintained on the black disk, careful attention being paid to the appearance of the hoop, the latter will be seen to assume one or other of the two forms illustrated.

If a point at 9 o'clock or 3 o'clock on the hoop is fixated, a single disk is *never* seen in the centre of the hoop. If the disk is seen as single it is always offset from the centre, and if it is seen as double the two disks are disposed one on each side of the centre.

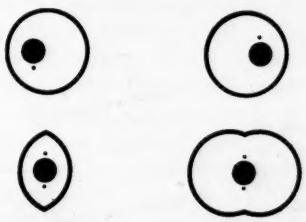


FIG. 11.—Experiment 11. When the disk is fixated and the depth effect is present, the appearance will be that of one or other of the lower figures. If a point on the periphery at 9 o'clock or 3 o'clock is fixated, then the disk will appear either as double, or as single and displaced from the centre.

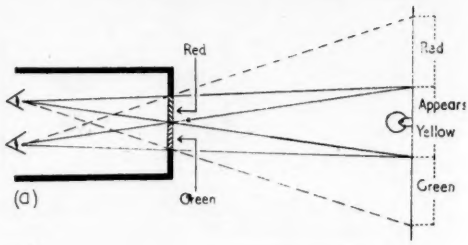
Experiment 12 (Fig. 12)

Part 1. Hecht's experiment.—Red and green filters are arranged in a box as shown in the diagram (Fig. 12), and the eyes look through these filters at a 500-watt lamp which projects through a sheet of white cardboard. The lamp and the area of cardboard round it are seen by the right eye through the green filter and by the left eye through the red filter. The responses of observers vary somewhat, but typically three squares are seen, a yellow one in the centre where red and green fields overlap, a green one on the right, and a red one on the left.

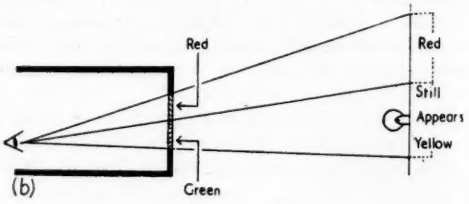
Part 2. To show that the yellow appearance is not due to binocular mixture.—The experiment is repeated and when the yellow square in the centre is clearly perceived, the observer closes his left eye. Surprisingly, no change in colour is observed, although the white surface is now being seen through nothing but a green filter.

Part 3. To show that the yellow colour is caused by the brightness of the lamp affecting the view through green filter.—Still using the right eye only, the observer moves the box so that the lamp is in line with the red glass. Immediately the cardboard viewed through the green glass appears as a rich green; the change in colour is very striking.

(*a*) When both eyes are open, the colour appears yellow where the fields overlap.



(*b*) With the left eye closed, the field seen by the right eye through the green glass still appears yellow.



(*c*) The apparatus is now moved so that the lamp is still seen by the right eye, but through the red glass; the field seen through the green glass now appears truly green.

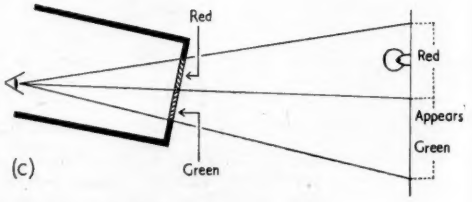


FIG. 12.—Experiment 12.

Discussion

Experiment 1.—A perfectly normal picture is seen of a lady cooking over a stove. Since it is certain that the portions of white ground corresponding to lady and fire are completely suppressed, the experiment demonstrates that normal vision may occur while there is suppression in each eye. This result accords well with the theory of du Tour (1760) that one of a pair of corresponding points is always suppressed by the other.

If it is held that in normal vision there is some fusion or addition of impulses from corresponding points of the two retinae, then it must be supposed that the striking suppression shown in this experiment is an abnormal occurrence evoked by the particular experimental arrangement. That such an inhibitory mechanism could lie dormant and disused all one's life to emerge with full efficiency the first time that an experiment of this kind is performed, seems extremely unlikely.

Experiment 2.—When the two pictures of the small model archway are combined the images on the retinae of the observer are identical with those which would be there if he looked at the model under normal conditions. Furthermore an equivalent experiment may be performed by looking at a real model without a stereoscope (for this purpose a reel of selotape may conveniently be substituted for the archway); precisely the same result occurs.

This experiment demonstrates that suppression and the depth effect can occur together under normal conditions of vision.

Experiment 3.—Since the dot appears above the vertical line in the combined view, it is clear there has been no change in the correspondence of points in this region.

In the combined view the vertical member suffers rivalry and appears as either a thick or a thin line, showing that the vertical thin line of the left picture and the vertical thick line of the right picture both fall on corresponding points. Thus the combination of the two pictures and the emergence of the depth effect have caused no change in the correspondence of the retinal elements.

The fact that the depth effect can be seen at periods during the rivalry when the vertical line appears thin shows that it can occur during suppression, while the fact that it can be seen at periods during the rivalry when the vertical line appears thick shows that the depth effect can still exist when the disparity is so great as to cause diplopia. This accords with the results of Tschermak and Höefer (1903) and of Wright (1951).

Wheatstone (1838) used this experiment to argue that there was no fixed set of correspondences between points. Hering (1861) maintained that correspondence was rigidly maintained and that suppression of the vertical line of the right picture occurred, but he denied that there was a genuine stereoscopic effect!

Experiment 4.—(*a*) The combined picture consists of a single disk, above which are seen a line and a square well separated from each other. Here both square and line suppress the corresponding portions of white ground in the same way as did the lady and the fire of Fig. 1.

(*b*) This corresponds to Fig. 4(*a*) except that disks are substituted for the square and the line. From the usually accepted theory that the single upper disk which is perceived results from the ' fusion ' together of the upper disk on each retina, it must follow that there is a change in the correspondence of elements in this region.

(*c*) This indicates that there is no change in correspondence at any rate of those points which are situated just outside the right upper disk.

On the suppression theory the explanation will be that correspondence is rigidly maintained, and that a single upper disk is seen because one of the two is suppressed.

The Two Kinds of Suppression.—The first kind was illustrated by the lady and the fire of Fig. 1, and is characterized by the fact that the figure suppresses the ground. In the past the existence of this kind of suppression has been surprisingly neglected. Thus, supposing a patient under orthoptic treatment sees the whole of the parrot and of the cage, then normally it would be said that there is no suppression, although as we have seen, some white ground is completely suppressed in each eye. However, if, for example, part of the parrot appears to be missing, then it is usual to say that there is suppression. What has in fact happened is that the usual direction of the suppression has been reversed, so that now the ground suppresses the figure. This constitutes a second kind of suppression. Experiments show that in general both black and white in the neighbourhood of a contour possess an enhanced value which enables them to suppress whatever falls on the corresponding points of the other retina. Suppression of the second kind occurs when elements of ground possessing such enhanced powers seen by one eye suppress all or part of the figure seen by the other eye.

Role of the Two Kinds of Suppression.—Now, on the fusion theory these two kinds of suppression are mechanisms which are exercised only under artificial conditions, as when looking at dissimilar drawings in a stereoscope. On the suppression theory, each mechanism plays an important part in the normal visual process. Consider, for example, Fig. 4(*b*): here both kinds of suppression occur; firstly the upper disk seen by the right eye appears in the combined view to be completely black, having entirely suppressed the corresponding white ground; this kind of suppression eliminates the appearance of any intermediate hues such as grey, which would appear if any fusion occurred from corresponding points. Secondly, the upper disk seen by the left eye has been entirely suppressed because the white ground near the upper disk of the right picture possesses enhanced powers of suppression by virtue of its proximity to this disk. This kind of suppression eliminates the diplopia which would result if in each case the black disk suppressed the white ground. Now, although a stereoscope has been employed, the retinal images are just those which would be formed if black spheres suitably arranged in space were viewed with both eyes, and the mechanisms invoked are just those which will apply under normal conditions. In the example given above there were two quite distinct suppressions, namely suppression of ground and suppression of object, and these two separate suppressions are necessary to avoid the occurrence of intermediate hues and of diplopia respectively. In other cases there may be no clear distinction into object and ground, but whenever there is disparity of the image, to avoid the two defects mentioned, these same two distinct processes

of suppression must occur. This is perhaps best expressed by saying that whenever there is disparity of a contour, then the contour and the area adjoining it on *both* sides in the one eye will suppress the corresponding points in the other eye. If the area involved on either side of the suppressing contour is sufficient in extent, the disparate contour in the other eye will be suppressed, and single vision will result.

Experiment 5.—This is similar to Experiment 4(*c*), and shows that there is no change of correspondence of elements in the neighbourhood of either of the disks, and that correspondence is rigidly maintained.

Experiments 6 and 7.—In previous experiments the suppression of the upper disk of the left picture has been inferred from its failure to appear in the combined view. Here, during the slow downward movement of the eyes, this disk can be seen to fade out slowly, thus enabling the actual process of suppression to be witnessed as it occurs. The fusion theory anticipates a sideways movement of the disks towards each other, but no such movement is observed.

A Possible Objection.—It could be argued that as the upper disk of Fig. 6 gradually fades out, so the points which receive the image of this disk on the left retina change their correspondence one by one. Thus, with the eyes in the upper position, the upper black disk of the left picture would correspond with the dot and the surrounding white area in the right picture; then as the eyes are lowered, so the correspondences might change in such a way that when the lower disks are fixated, the upper black disk in the left picture would fall on retinal areas corresponding to those receiving the image of the upper black disk of the right picture. The faded disk would correspond to the condition when some of the points had changed their correspondences and others had not. Experiment 8 was designed to give evidence on this point.

Experiments 8 and 9.—On the fusion theory, to explain the nearness of the nearest disk, the upper disk of the left picture is supposed to fuse with the left upper disk of the right picture, and the retinal elements must be supposed to change their correspondence accordingly. Similarly, to explain the remoteness of the furthermost disk, the upper disk of the left picture now has to fuse with the right upper disk of the right picture, and again the retinal elements must be supposed to change their correspondence accordingly. Thus, to explain the apparent position in space of both upper disks, two sets of correspondences will have to exist simultaneously. It is scarcely conceivable that such a mechanism could exist, especially since a situation requiring this feat hardly ever occurs in real life.

On the suppression theory it is necessary only to suppose that the upper disk of the left picture is suppressed.

Experiment 10

Part 1.—This experiment is based on one described by Panum (1858). The fact that the apparent separation is that of either the left or the right pair obviously lends support to the suppression theory. The subsidiary marks assist the observation that the right line of either the left or the right diagram is suppressed.

Part 2.—Panum interpreted this result as disproving the suppression theory. He thought that since the vertical lines appeared widely separated the space between them must appear wholly of the colour of the left card, i.e., red. This rejection of the theory must be criticized on two grounds:

(*i*) On the suppression theory: if, say, the left line of each card is fixated, then in one eye the right-hand line will be suppressed; if the suppression occurs in the right eye the lines will appear widely spaced. The whole of the ground in between need not, however, appear entirely red, though clearly part of it must do so.

(*ii*) With shades of red and blue so chosen that now one and now the other predominates in the process of rivalry, it is most interesting to notice how well the two changes occur together. If the ground of the left card is made blue, and that of the right card red, then the ground in the combined picture will appear now mainly blue with the lines closely spaced, now motley with the lines still closely spaced, now motley but with the right-hand line seen double, and finally, as the innermost one fades, the ground becomes predominantly red.

Experiment 11.—When the disk is fixated, the two alternative appearances of the hoop are clearly due to suppression either of the inner or of the outer halves of the circles. The disk may also appear in a circular hoop, and displaced either to the right or the left. This corresponds to suppression of both the disk and the hoop of one or the other picture.

With points fixated at 3 o'clock or 9 o'clock on the periphery, the disk appears to the left or right of the centre according as the disk of the right or the left picture is suppressed. If neither disk is suppressed, then two disks are seen, one on each side of the centre.

It is important to notice that the disk never appears in the centre of a circular hoop, as the fusion theory would lead one to expect.

It may happen that an observer seeing figures of this type may see the disk as displaced from the centre by an amount intermediate between the displacements in the two separate pictures. This finding appears at first sight to be opposed to the suppression theory, and Experiment 11 was designed to investigate this effect. The phenomenon always fails to appear when subsidiary marks are used to ensure accurate fixation, and the effect may accordingly be ascribed to failure to maintain fixation accurately.

Binocular Colour Mixture.—According to the suppression theory, one of a pair of corresponding points always suppresses the other, and it would consequently be anticipated that binocular mixtures of colours could not occur. Since, however, there is a considerable body of evidence to support the view that these mixtures can in fact be produced (Meyer, 1856; Trendelenburg, 1914; Hecht, 1928; Prentice, 1949; Hurvitch and Jameson, 1951), it is important to examine the evidence carefully.

If an attempt is made to combine two different colours in the stereoscope, the usual result is not fusion, but rivalry.

In the arrangement due to Meyer (1856), one eye sees a square of which the left half is yellow and the right half blue, while the right eye sees a red square. The yellow and blue remain distinct in the neighbourhood of the boundary, but further out, although there is much rivalry, some sort of mixture with red does appear to occur; the appearance, however is peculiar, impossible to describe in words, and unlike uniocular mixtures.

It is suggested in these cases only one of each pair of corresponding points conveys its colour impression to the mental picture, the other being suppressed, but that in each eye the dominant and suppressed points are so closely intermingled that a mental picture of very fine grain is formed. Thus both colours appear to be seen simultaneously in the same place but yet not to be properly mixed. The half-faded disk in Experiment 6 represents a binocular mixture of black and white of this kind.

Experiment 12.—The experiment of Hecht (1928) stands in a different category. The yellow which is seen has none of the peculiar shifting appearance of the other allegedly binocular mixtures, but on the contrary is quite stable so that the experiment seems at first sight to be entirely convincing.

Part 2 of Experiment 12 shows, however, that this yellow is not due to binocular mixture, and Part 3 shows that the yellow colour is actually caused by the brightness of the lamp affecting the hue and saturation of what is seen by the right eye through the green filter. This apparently yellow patch suppresses the corresponding red area on the left retina.

If Hecht's experiment is repeated, omitting the lamp and using only a plain white surface, the stability is lost, there is much rivalry, and any apparently binocular mixture has the same peculiar characteristics as those obtained by the other methods.*

On the whole, then, although the picture is far from clear, the results of binocular colour-mixture experiments appear to favour the suppression theory.

Depth Perception with Diplopia.—Tschermak and Hoefer (1903) and Wright (1951) have given evidence that some sense of depth is conferred by the disparity clue even when this is so great that diplopia occurs. Loewenstein (1952) has made the important observation that a depth effect is present even in Fig. 4(*a*). These results, which are impossible to explain by the fusion theory, do not oppose the suppression theory.

Suppression when Identical Portions of the Image fall on Corresponding Points.—The problem of whether suppression occurs when there is no disparity and identical stimuli fall on corresponding points is quite separate from those we have considered so far.

In a brilliant paper, du Tour (1760) described a series of simple experiments to show that when *dissimilar* stimuli fall on corresponding points only one of them is perceived. He then wrote:

> Si les faits que je viens de rapporter concourent à établir que de deux objets qui se peignent dans les yeux il n'y en a qu'un seul qui affecte l'âme quand leurs images tombent, ou au points des retines où les axes optiques aboutissent, ou sur des points correspondans entr'eux, à plus forte raison serons nous fondés à admettre qu'un même objet ne peut produire en pareil cas qu'une seule impression efficace sur l'âme, quoiqu'il se peigne en même temps dans l'un et l'autre oeil.

Thus he argued that since one of two dissimilar images on corresponding points always suppresses the other, so also must one of two similar images do likewise. This is evidence but it is not proof.

*No attempt is made here to explain the peculiar and important result of Hurvitch and Jameson (1951), who claim to have produced white from a binocular mixture of red and green.

The Logarithmic Argument.—Let us now suppose that there was a confluence of the visual pathways, and that the fusion took the form of a simple addition of the frequency of the action potentials, as would occur if fibres carrying impulses originating at corresponding points converged upon a single destination. It is instructive to calculate on this basis what would be the expected increase in brightness of an object viewed with one eye or with two. Experiments have shown that the frequency of the discharge is proportional to the logarithm of the physical intensity of the light stimulus. Also it is found that if a filter of Neutral Density 4 is placed in front of the eye under normal daylight conditions, then vision is possible through it without dark adaptation, *i.e.*, this gives very roughly threshold intensity. The filter allows $1/10^4$ of the light to pass through, so that its removal increases the light intensity by 10^4 times, and this results in a certain rate of discharge in the optic nerve. It follows that to double this rate of discharge it is necessary to double the logarithm, of the light intensity, *i.e.*, to increase it by a further factor of 10^4. To do this would require an intensity of illumination equal to ten thousand times normal daylight. Now, opening or closing one eye while the other remains open causes scarcely any change in brightness of the object viewed, so that any simple fusion of the kind supposed is definitely excluded.

The Argument from Dissimilar Stimuli.—If it be taken as established for the case of disparity of the retinal images that one of each pair is always suppressed when dissimilar images fall on corresponding points, then separate evidence is required to show that suppression does not occur when similar stimuli fall on corresponding points. It seems that there is no good evidence to indicate this absence of suppression, and from the principle of economy of hypothesis, we should assume, at any rate provisionally, that suppression occurs in both cases.

Statement of the Suppression Theory of Binocular Vision

The correspondence of the retinal elements is completely rigid and unchanging.

One of a pair of corresponding points always suppresses the other.

Where there is a contour, the suppressing power of retinal elements on each side of it is enhanced.

Where there is disparity of contour, then in the one eye retinal elements on *both* sides of this contour will suppress corresponding points in the other eye.

If the extent of the suppression is smaller than the disparity between the contours, then diplopia occurs, but depth perception is possible.

If the extent of the suppression is greater than the disparity between the contours, one contour is suppressed and single vision occurs with depth perception.

The contour of one part of the image may be dominant in one eye, and that of another part may be dominant in the other eye.

Summary

The theory is advanced that of a pair of corresponding points, one always suppresses the other.

Evidence to support this view is obtained by combining various line diagrams in a stereoscope and noting which portions are suppressed.

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REFERENCES

DUNLAP, K. (1944). *Amer. J. Psychol.*, **57**, 559.
HECHT, S. (1928). *J. gen. Physiol.*, **11**, 255.
HEINE, L. (1900). *v. Graefes Arch. Ophthal.*, **51**, 146.
HERING, E. (1861). "Beiträge zur Physiologie". Englemann, Leipzig.
HURVITCH, L. M., and JAMESON, D. (1951). *Science*, **114**, 199.
LOEWENSTEIN, O. (1952). Personal communication.
MEYER, H. (1856). *v. Graefes Arch. Ophthal.*, **2**, Part 2, 77.
PANUM, P. L. (1858). "Physiologische Untersuchungen uber das Sehen mit zwei Augen". Schwerssche Buchhandlung, Kiel.
Prentice, W. C. H. (1948). *J. exp. Psychol.*, **38**, 284.
SHERRINGTON, C. (1906). "The Integrative Action of the Nervous System", ed. 1947, p. 353. Cambridge University Press.
DU TOUR, E. F. (1760). "Mémoires de Mathématique et de Physique". Présentés à l'Académie Royale des Sciences, **3**, 514.
TRENDELENBURG, W. (1914). *Z. Sinnesphysiol.*, **48**, 199.
TSCHERMAK, A., and HOEFER, P. (1903). *Pflugers Arch. ges. Physiol.*, **98**, 299.
WHEATSTONE, C. (1838). *Philos. Trans.*, **128**, 371.
WRIGHT, W. D. (1951). *Proc. phys. Soc. B., Lond.*, **64**, 289.

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EXUDATION AND ABSORPTION MECHANISMS OF THE NORMAL CONJUNCTIVAL CAPILLARIES*

BY

K. H. GO

Formosa

IT is still not clear how the cornea which has no vessels in its tissue is nourished, but the problem of the nutrition of tissue is closely related to the vascular structure, so that if we wish to solve the problem of corneal nutrition we must examine the construction and functions in normal and abnormal situations of the finest conjunctival capillaries at the limbus terminating in the end-capillaries.

Following up this point, before entering upon the study of the cornea, I examined the end-capillaries of the limbus *in vivo* with a slit lamp to discover their construction and function. A special enquiry was made into the exudation and absorption mechanisms, and the results of these investigations are presented below.

Material and Technique

The construction, blood stream, tonus, and exudation and absorption mechanisms of the end-capillaries of the limbus were examined by inserting a drop of dionine 0.5–3.0 per cent., pilocarpine 0.5–1.0 per cent., histamine 0.5–1.0 per cent., adrenaline × 5000, and atropine 0.1–1.0 per cent.

The temperature of the solutions was that of normal blood heat. The patients were young men (15 to 25 years old) with no disease of the eyes. The slit lamp was not very brightly illuminated and the field of the microscope was irradiated with the reflex light coming from the surface of the iris.

Results

The original anatomical construction of the end-capillaries is the same as that of the capillaries in the skin papillae. They end in a bow shape and have one arterial and one venous shank. Sometimes they have two or three venous shanks; but the arterial capillaries never terminate at the end of the arterial shank but have a returning venous shank. It is easy to distinguish both types of shank by the flow of blood.

The blood streams in the capillaries are not permanent and sometimes the capillaries contain no blood. The various blood streams may be seen in the same field of vision of the microscope. Eight types of capillary were distinguished:

continuous non-granular	intermittent granular
wavy	beadlike (globular)
intermittent non-granular	static
continuous granular	blood-free

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A physiological oedema of the epithelium (Vogt, 1931) may be seen in the peripheral portion of the normal cornea. This phenomenon is caused by the infusion of lymph coming from the end-capillaries.

(1) *Instilling one drop Dionine (3 per cent.)*

The capillaries dilated promptly and all now contained a blood stream. The blood streams changed to the rapid continuous non-granular type.

After 2 minutes the fine grey-white spots were beginning to ooze from the arterial shanks and then from the venous shanks and transitional portions. The shank seemed just like a stamen with its pollen. The oozing gradually spread to the nearby tissue, and was thick especially at the branched portion. After about 25 minutes on an average, the exudation reached the maximum, the region of the capillaries was diffusely muddy and was lined from the clear cornea for a little way from the top of the shanks. After about 30 minutes the arterial shanks contracted and the blood streams grew slower and more granular, sometimes static. After about 60 minutes the region of the capillaries grew clearer, the arterial shanks were dilating, the stasis disappeared, and the blood streams were becoming quicker and more granular. After about 120 to 150 minutes, the absorption mechanism had ceased to operate and everything became normal.

(2) *Instilling one drop Histamine (1 per cent.)*

The capillaries dilated promptly. The blood streams changed to the rapid continuous non-granular type. After 20 to 30 minutes the *Epithelbetauung* of the region of the capillaries grew clearer, but the fine grey-white spots did not appear. After about 30 minutes, the arterial shanks were contracting a little and the blood streams became slower and more granular, sometimes static. Then the arterial shanks became dilated, and the blood streams grew quicker, and after about 100–120 minutes everything became normal.

(3) *Instilling one drop Pilocarpine (1 per cent.)*

The capillaries dilated promptly, and the blood streams changed to the rapid continuous non-granular type, but the fine grey-white spots did not appear, and the *Epithelbetauung* was not clearer than that seen with histamine. After 30–50 minutes the effect of the pilocarpine wore off and everything became normal.

(4) *Influence on the Action of Dionine of Adrenaline (5000X), and of Eserine (1 per cent.), Atropine (1 per cent.), or Cocaine (1 per cent.)*

(*a*) *Dionine plus Adrenaline.*—About 60 per cent. of the capillaries dilated slowly, but at different times. Some of the arterial shanks were contracted, blood free, and static. In the dilated capillaries the blood streams changed to the rapid continuous non-granular type. After 2–3 minutes the fine grey-white spots appeared from the dilated capillaries, but not from those which were unchanged or constricted.

(*b*) *Dionine plus Eserine (1 per cent.), Atropine (1 per cent.), or Cocaine (1 per cent.)* The capillaries dilated whether the dionine was instilled before or after the eserine, atropine, or cocaine. The exudation appeared, and the effect of the dionine was not disturbed.

Discussion

(1) The results show that by instilling one drop dionine the mechanism of exudation and absorption from the capillaries can easily be set in motion within 2 minutes. The exudation-period can be distinguished from the absorption-period as follows:

(*i*) During exudation the capillary is dilated, and the blood stream is rapid.

(*ii*) During absorption the arterial capillary is slightly contracted and the blood stream is slow at first; then both gradually return to normal.

Histamine causes only slight exudation from the capillary and does not cause the grey-white spots of oozing.

Pilocarpine causes hardly any exudation from the capillary.

Adrenaline can hinder the action of dionine, but atropine, eserine, and cocaine do not.

(2) For a histological examination of the fine grey-white spots we can refer to Nakamura (1937), who examined a section of the ocular and peri-corneal conjunctival tissue after inserting one drop dionine. The epithelium of the conjunctival tissue was swollen, and the conjunctival capillaries were dilated and filled with leucocytes just like the lymph-capillaries. The leucocytes not only filled the capillaries but penetrated the nearby tissue. About 90 per cent. were eosinophil leucocytes.

The fine grey-white spots are therefore eosinophil leucocytes, and the *Epithelbetauung* are the *Epithelödem* from the end-capillaries (Vogt, 1931).

(3) The capillary must be dilated in order to cause exudation, and slight contraction of the arterial capillary always causes absorption. This is clearly shown if adrenaline is used to hinder the action of dionine. Krogh (1929) reports the same results in the examination of animals, in that when the blood stream is fast the exudation appears and when it is slow absorption occurs. Krogh describes how the arrested blood stream causes an increase of the permeability of capillaries, and Ricker and Regendanz (1921), who examined the conjunctival vessels of the rabbit, describe how when the blood stream is arrested the exudation does not occur and the *postrubrostatischer Zustand* is the same as the *leucodiapedetischer Zustand.* They say that the leucodiapedesis can be seen only in the larger vessels with an axial stream and a wall stream; it is never seen in the capillaries, and it occurs only when the blood stream is slow.

(4) The function of the vessels is governed by the vasomotor nerves. Adrenaline, atropine, pilocarpine, and cocaine do not cause exudation from the capillaries, and adrenaline hinders it even when the exudation mechanism has been operating. If one drop of adrenaline be instilled during absorption, the arterial shanks, already slightly contracted, contract spasmodically and the absorption mechanism has more time for its recovery process than when

dionine only is used. It appears that this slight contraction of the arterial capillaries during absorption is caused by the sympathetic nerve being slightly stimulated by the exudate. Adrenaline can excite the endings of the sympathetic nerves, and pilocarpine and atropine have an effect upon the para-sympathetic nerves. These do not cause exudation. Therefore both exudation and absorption are caused by the alteration of the nature of the capillary wall. The vasomotor nerves have no primary or active effect upon the capillaries in these processes.

Summary

When one drop of dionine is instilled into the conjunctival capillary the following results are observed:

(1) The exudation mechanism is set in motion when the capillary is dilated, and the blood stream is fast.

(2) The absorption mechanism acts through the venous shank of the capillary when the arterial shank is slightly contracted and the blood stream is slow or static.

(3) Both mechanisms are caused by an alteration in the capillary wall which is effected by the direct action of specific substances.

(4) The leucodiapedesis caused by dionine appears from the capillary as a grey-white spot during exudation, and returns through the venous shank of the capillary during absorption.

REFERENCES

COHNHEIM, J. (1867). *Virchows Arch. path. Anat.*, **40**, 1.

KROGH, A. (1929). "The Anatomy and Physiology of Capillaries", 2nd ed. Yale University Press, New Haven.

LANDIS, E. M. (1927). *Amer. J. Physiol.*, **82**, 217.

MÜLLER, O. (1937–39). "Die feinsten Blutgefasse des Menschen", vols. 1 and 2. Enke, Stuttgart.

NAKAMURA, Y. (1937). *Acta. Soc. opthal. jap.*, **41**, 104.

RICKER, G., and REGENDANZ, P. (1921). *Virchows Arch. path. Anat.*, **231**, 1.

VOGT, A. (1931). "Lehrbuch und Atlas der Spaltlampen-mikroskopie des lebenden Auges", 2nd ed. Springer, Berlin.

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INFLUENCE OF THE THIRD CRANIAL NERVE ON INTRA-OCULAR PRESSURE*

BY

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THE adrenergic sympathetic system has been shown to exert a considerable effect on the intra-ocular pressure (Greaves and Perkins, 1952). We know, however, that cholinergic drugs are often effective in lowering the intra-ocular pressure in glaucoma so that it is possible that the parasympathetic system may also play a part in the control of the tension of the eye. Since the third cranial nerve carries the parasympathetic supply to the intra-ocular musculature, it is logical in the first place to determine whether it is also responsible for the cholinergic control of the intra-ocular circulation.

The literature on this subject is small. Henderson and Starling (1904), after some careful experiments, concluded that the third cranial nerve had no effect on the intra-ocular pressure. Schmerl and Steinberg (1950) however, reported that electrical stimulation of the ciliary ganglion in the rabbit caused a rise, and cauterization of the ganglion caused a fall, in the intra-ocular pressure. They used a blind approach to the ganglion, passing a curved electrode round the globe and recording the changes in the intra-ocular pressure with a Schiötz tonometer. In view of the technique employed and the absence of simultaneous recordings of the general blood pressure, we feel that their results should be viewed with caution.

The parasympathetic outflow to the eye, so far as the third nerve is concerned, originates

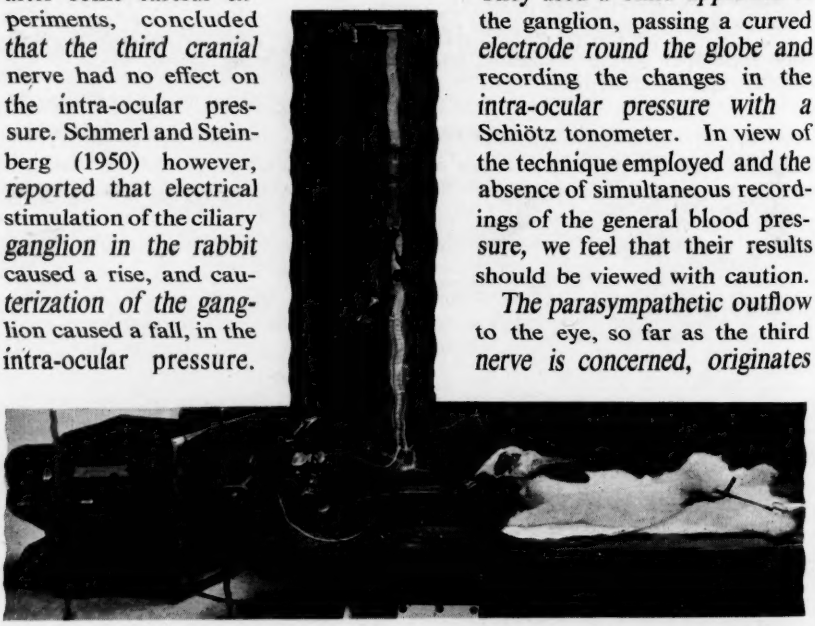

FIG. 1.—General view of apparatus for recording intra-ocular pressure and femoral blood pressure.

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in the midbrain in close association with the nucleus of the third nerve, and travels along this nerve to the ciliary ganglion, whence it reaches the eye by way of the short ciliary nerves. In the rabbit the ciliary ganglion and orbital portion of the third nerve are relatively inaccessible without causing considerable upset to the vascular supply and venous drainage of the eye. We have therefore exposed the third nerve in its intracranial course, an approach which can be facilitated by decerebration.

Methods

Rabbits were anaesthetized with nembutal intravenously, 1 gr. per 5 lb. body weight. The skin and muscles were reflected off the cranium and the skull opened with a trephine. This opening was enlarged with bone nibblers until the cerebral hemispheres could be freed and either removed or elevated to expose the third nerves in their course on either side of the pituitary fossa. Bleeding from the circle of Willis was a frequent complication and great care was required to isolate the nerve without causing profuse haemorrhage.

The nerve could now be cut and stimulated by applying a bipolar electrode connected to an electronic stimulator giving a square wave, 50 cycles/sec. at 4 volts (Attree, 1950).

The intra-ocular pressure was measured by the manometer described in a previous paper (Greaves and Perkins, 1951) whereby simultaneous records of the intra-ocular pressure of both eyes and the general blood pressure were made.

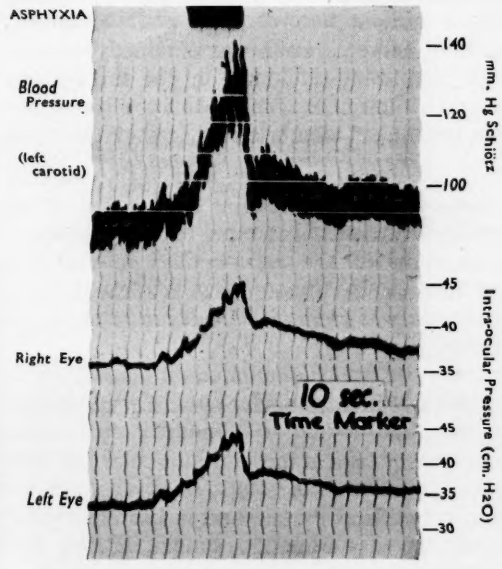

FIG. 2.—Typical tracing showing variations in intra-ocular pressure and blood pressure during asphyxia.

Fig. 1 shows the general arrangement of the apparatus. *Fig. 2 shows a typical tracing* made by this method and which illustrates well how the intra-ocular pressure varies with the general blood pressure.

Results

(1) Effects of Decerebration.—As decerebration was usually performed before the intra-ocular pressure and blood pressure *tracings were started, it was* thought advisable to do *two control experiments in* which the intra-ocular pressure and blood pressure were recorded during the actual procedure of decerebration so that any variation produced by the operation could be observed. In one of these *experiments it was found that, apart from a temporary disturbance during* the manipulations, the blood pressure and intra-ocular pressure soon settled down to their previous level. In the other experiment the blood pressure

dropped by some 20 mm. Hg with a corresponding fall in the intra-ocular pressure following a rather profuse haemorrhage from the circle of Willis. It would therefore appear that, provided severe haemorrhage can be avoided, decerebration has little influence on the results of the experiments. Further confirmation of this was given by three experiments in which the nerve was exposed without decerebration, the results differing in no way from those obtained in the decerebrate animal.

(2) Section of the Third Nerve

(*a*) *Acute Experiments.*—The intra-ocular pressure was observed for periods up to 30 min. in each of four animals in which one or both third nerves had been cut. In two cases, no significant change in the intra-ocular pressure was observed. In one case section of the nerve was followed by a rise in the intra-ocular pressure. In this experiment haemorrhage round the nerve occurred during the exposure and section, and a plug of cotton wool which was used to stop the bleeding probably interfered with the venous return from the eye, for on its removal the intra-ocular pressure returned to normal. In another animal a slow fall of 2 cm. saline was recorded.

(*b*) *Survival Experiment.*—In one rabbit the third nerve was approached and cut under aseptic conditions without decerebration and the animal allowed to recover. Complete third nerve paralysis was obtained, but over a period of several months no significant difference in the intra-ocular pressure between the two eyes could be detected. The aplanation tonometer of Maurice (1951) and a Schiötz instrument were used to measure the intra-ocular pressure.

(3) Stimulation of the Third Nerve.—In all experiments stimulation of the third nerve using 4 volts at 50 cycles/sec. resulted in a rapid rise in intra-ocular pressure accompanied by contraction of the extra-ocular muscles and sphincter pupillae. The rise in intra-ocular pressure was greatest initially, tending to decrease while the stimulus was maintained, but not returning to normal until the stimulation ceased.

In view of the possibility that this rise, which amounted on the average to 5 cm. saline, was due to contraction of the extra-ocular muscles, experiments were carried out with decamethonium iodide to eliminate this factor. Decamethonium iodide paralyses transmission at the neuromuscular junction, in this respect resembling curare. It differs from curare, however, in that it has an initial stimulating action on skeletal muscle and is less effective in producing blockage of transmission in autonomic ganglia (Paton and Zaimis, 1948; 1949).

We found that an average dose of 0.4 mg. decamethonium iodide injected intravenously into a rabbit resulted in paralysis of the extra-ocular muscles after an initial tonic contraction. This latter effect had been previously noticed in isolated preparations of the superior rectus muscle in the rabbit (Ambache, 1952).

In a decerebrated animal the third cranial nerve was stimulated in order to verify that it was intact. 0.4 mg. decamethonium iodide was then injected intravenously. After an interval of 4 minutes from the injection, stimulation of the third nerve produced good miosis but no contraction of the extra-ocular muscles and no significant change in the intra-ocular pressure (Fig. 3). This experiment was repeated in four other animals with similar results.

It therefore appears that stimulation of the third nerve in normal rabbits has no effect on the intra-ocular pressure except insofar as it causes contraction of the extra-ocular muscles.

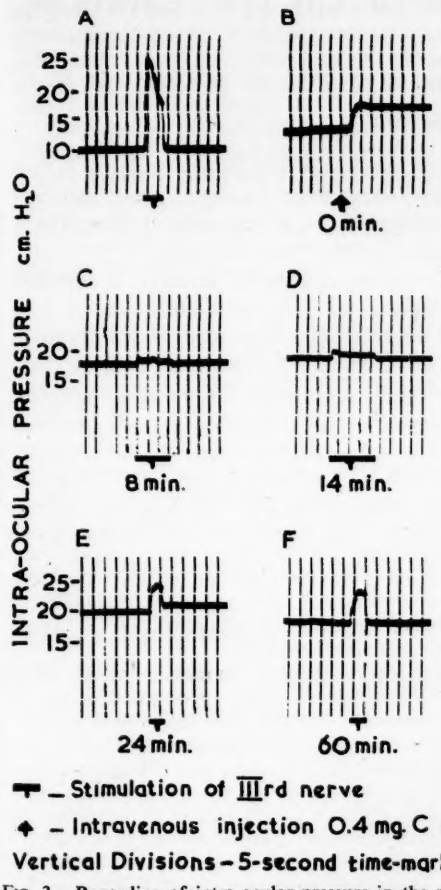

FIG. 3.—Recording of intra-ocular pressure in the right eye during stimulation of the right IIIrd nerve.

A, before administration of decamethonium iodide (C10)
C, D, E, F, after administration of C10
B, effect of intravenous injection of 0.4 mg. C10.
Blood pressure remained constant throughout.

Summary

(1) Section of the third cranial nerve in rabbits has no significant effect on the intra-ocular pressure.

(2) Stimulation of the same nerve produces a rise in intra-ocular pressure which is due to contraction of the extra-ocular muscles.

(3) After paralysis of the extra-ocular muscles by decamethonium iodide, stimulation of the third cranial nerve causes no change in the intra-ocular pressure.

REFERENCES

AMBACHE, N. (1952). Personal communication.
ATTREE, V. H. (1950). *J. sci. Instrum.*, **27**, 43.
GREAVES, D. P., and PERKINS, E. S. (1952). *British Journal of Ophthalmology*, **36**, 258.
HENDERSON, E. E., and STARLING, E. H., (1904). *J. Physiol., Lond.*, **31**, 305.
MAURICE, D. M. (1951). *British Journal of Ophthalmology*, **35**, 178.
PATON, W. D. M., and ZAIMIS, E. J. (1948). *Nature, Lond.*, **162**, 810.
——— ——— (1949). *Brit. J. Pharmacol.*, **4**, 381.
SCHMERL, E., and STEINBERG, B. (1949). *Amer. J. Ophthal.*, **32**, 947.

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CASE NOTES

SPONTANEOUS RUPTURE OF THE LENS CAPSULE*

BY

J. GRAHAM SCOTT

Johannesburg

SINCE the first reports of spontaneous rupture of the lens capsule by Ulrich (1882) and Szily (1884), further cases have been reported by Rollet and Genet (1913), Gonzalez (1919), Kaufman (1933), Knapp (1937), Box (1941), Sugar (1949), and Bonavolonta (1950).

Rupture of the lens capsule also occurs in anterior lenticonus (Ehrlich, 1946), and after trauma (Bellows, 1944).

The purpose of this paper is to describe one new case of spontaneous lens rupture, and two others which occurred many years after trauma; and also to discuss the glaucoma which followed the lens rupture in all reported cases but one (that of Box, 1941).

Case Reports

Case 1, male, aged 70, had bilateral senile cataract and the left lens was removed successfully 10 years ago. I first saw him in May, 1946, when he came to discuss operation on the right eye. The right cataract was mature, and the eye otherwise normal. The anterior chamber was of normal depth and there was good light projection. Operation was postponed owing to bronchitis, and in February, 1947, after the excitement of running for and missing a bus, the patient felt a sudden pain in the right eye. Despite rest and heat to the eye, the pain persisted and made him sick.

When examined 2 days later the right eye was red, tension was raised, and iris details were obscured by a milky fluid which filled the anterior chamber. There were no keratic precipitates and the eye did not respond to eserine. A broad iridectomy was done under general anaesthesia the following day. When the counter puncture was made, milky fluid was seen to escape and the iris pattern immediately became apparent. The patient made a good recovery and a month later reported improvement in vision. Tension was normal. The outline of the upper third of the nucleus could be clearly seen as the upper part of the cortex had been absorbed. The eye remained quiet and the nucleus sank down in the capsule, with improvement of vision.

Fine keratic precipitates were noted in May, 1947, and the lens was removed without complication soon afterwards.

By the end of the year corrected vision had improved to 6/18 in the right eye, tension remained normal, and the eye was free from inflammation.

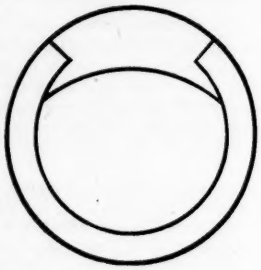

FIGURE.

Case 2, male, aged 53, had had an accident at work 4 years ago when he was hit on the forehead by a bar. He noticed failure of vision of the left eye 2 months later. The left cataract was held to be unconnected with the accident by the specialist who saw him at the time, as he had early senile changes in the right eye.

* Received for publication July 29, 1952.

I first saw him on September 20, 1948, when he complained of failing vision in the right eye and blindness of the left eye. The right eye had early lens changes. The left had a mature cataract, no keratic precipitates, and good projection of light. I saw him again 4 weeks later, having made enquiries about the old accident and re-examined him under a mydriatic.* He experienced a sudden pain in the left eye on the way home from work 3 days later. Pain persisted and he saw me the next day, October 20, with a hard, red, painful left eye, in which the iris was obscured by a milky fluid. There were no keratic precipitates.

Operation was not possible for a few days as he elected to go home, but a broad iridectomy was performed on October 26. After escape of the milky fluid, the iris became visible at once and he made an uneventful recovery. On November 8, 1948, the outline of the upper third of the nucleus could be faintly seen and some radial folds were noted in the capsule. Tension was normal and no keratic precipitates were visible.

I did not see him again but learned that he had no more pain in the eye before his death on March 9, 1949.

Case 3, male, aged 40, was hit in the right eye by a stone when at work in 1944. He was treated by Dr. Rosset-Berdez who was so kind as to send me a report that the vision was 6/6 4 months after the accident, and that there was no lens opacity, but a slight vitreous haze. Vision gradually failed and in 1946 traumatic cataract was diagnosed by Dr. Marais, who kindly read me his notes.

When I saw the patient in 1950, he complained that he had had annual attacks of redness of the right eye since 1946, each lasting about a week. He noted vision returning to the right eye 7 months ago, but it had clouded over again. My examination revealed a red, hard, painful right eye. There was a " hypopyon " of lens matter and the aqueous was full of white flakes.

The lens matter was washed out through a keratome incision and the eye gradually quietened. Considerable vitreous haze was found in the eye and vision has not been restored.

Tension has remained soft, and the eye is now aphakic, but the patient has had two attacks of iritis and wishes to have the eye removed.

Discussion

It is uncommon for glaucoma to follow needling of a congenital cataract but it is well known as a sequel to some cases of traumatic cataract, to many cases of exfoliation of the lens capsule (Vogt, 1925; Shapira, 1935; Hörven, 1937; Garrow, 1938), and to some cases of spontaneous resorption of senile cataract (Natanson, 1891; Mitvalsky, 1892; von Reuss, 1900; Gifford, 1900–1927; Verrey, 1916; Knapp, 1927; Daily, 1933; Bonavolonta, 1950). The reason given for the high incidence of glaucoma in exfoliation was that fine particles from the lens capsule gradually silted up the trabecular spaces but this is not now generally accepted. The explanation of glaucoma in cases of spontaneous resorption of a senile cataract has also changed since 1900.

Gifford (1900) used to believe that traction of the loose nucleus caused irritation of the ciliary process and rise of tension, but in 1918 he concluded that the cause was transudation of toxins liberated by the disintegrating lens and by blocking of angle with lens substance. Verhoeff and Lemoine (1922) agreed that a hypermature cataract was toxic but proved that there could

* I used eserine to counteract this.

also be an anaphylactic reaction to lens protein. This work was confirmed by Lemoine and Macdonald (1924).

Sugar (1949) suggested that spontaneous absorption of senile cataract was due to a minute posterior rupture of the capsule, but this attractive theory would not explain the case reported by Ballantyne (1926), where an anterior lens opacity was absorbed spontaneously leaving the clear posterior lens matter.

It would appear that a hypermature cataract is toxic and that glaucoma can be produced by the irritation of the toxin on the ciliary body. This rise of tension must be accelerated if, in addition to the toxic reaction, the angle of the anterior chamber is blocked by lens debris.

The combination of toxic reaction and angle blocking is the probable explanation of the glaucoma in spontaneous rupture of the lens capsule. There must also be cases where a sensitivity to lens protein is an additional cause.

Summary

(1) Three cases of spontaneous rupture of the lens capsule in cataract (one senile, two traumatic) are described.

(2) Each attack caused acute glaucoma with milky aqueous.

(3) In two cases, the eye remained quiet for many months with the nucleus retained; in the third case, there were recurring attacks of iritis.

REFERENCES

BALLANTYNE, A. J. (1926). *British Journal of Ophthalmology*, **10**, 202.
BELLOWS, J. G. (1944). " Cataract and Anomalies of the Lens ". Mosby, St Louis.
BONAVOLONTA, A. (1950). *Rass. ital. Ottal.*, **19**, 326.
BOX, W. M. (1941). *Med. J. Aust.*, **1**, 451.
DAILY, R. K. (1933). *Sth. med. J., Bgham., Ala.*, **26**, 396.
EHRLICH, L. H. (1946). *Amer. J. Ophthal.*, **29**, 1274.
GARROW, A. (1938). *British Journal of Ophthalmology*, **22**, 214.
GIFFORD, H. (1900). *Amer. J. Ophthal.*, **17**, 289.
——— (1918). *Ibid.*, ser. 3, **1**, 83.
——— (1927). *Arch. Ophthal., Chicago*, **56**, 457.
GIFFORD, S. R. (1925). *J. Amer. med. Ass.*, **85**, 351.
GONZALEZ, J. DE J. (1919). *Amer. J. Ophthal.*, **2**, 742.
HÖRVEN, E. (1937). *British Journal of Ophthalmology*, **21**, 625.
KAUFMAN, S. I. (1933). *Arch. Ophthal., Chicago*, **9**, 56.
KNAPP, A. (1927). *Ibid.*, **56**, 124.
KNAPP, H. C. (1937). *Amer. J. Ophthal.*, **20**, 820.
LEMOINE, A. N., and MACDONALD, A. E. (1924). *Arch. Ophthal., Chicago*, **53**, 101.
MITVALSKY, J. (1892). *Zbl. prakt. Augenheilk.*, **16**, 289.
NATANSON, A. (1891). *Klin. Mbl. Augenheilk.*, **29**, 423.
REUSS, A. VON (1900). *Zbl. prakt. Augenheilk.*, **24**, 33.
ROLLET and GENET (1913). *Rev. gén. Ophtal., Paris*, **32**, 1.
SHAPIRA, T. M. (1935). *Amer. J. Ophthal.*, **18**, 31.
SUGAR, H. S. (1949). *Ibid.*, **32**, 1509.
SZILI, A. (1884). *Zbl. prakt. Augenheilk.*, **8**, 17.
ULRICH, R. (1882). *Klin. Mbl. Augenheilk.*, **20**, 230.
VERHOEFF, F. H., and LEMOINE, A. N. (1922). *Amer. J. Ophthal.*, **5**, 700.
VERREY, L. (1916). *Ibid.*, **33**, 230.
VOGT, A. (1925). *Klin. Mbl. Augenheilk.*, **75**, 1.

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APPLIANCE

MODIFICATION OF BELL'S ERISOPHAKE*†

BY

ALBERT C. ESPOSITO

Huntington, West Virginia, U.S.A.

THE use of the suction cup to aid in the extraction of a cataractous lens has become very popular. Hulen (1911) recommended this method, and its use has been encouraged by the work of many surgeons, including the Barraquers, Dimitry (1933), Nugent and Fisher (1933), and Castroviejo. The Bell and Harrington erisophakes are now very frequently used.

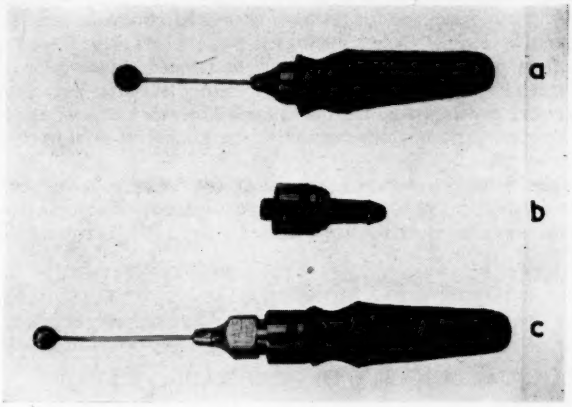

FIG. 1(*a*).—Contact lens suction cup, with needle as in the original Bell's erisophake.

(*b*).—B.D. adapter (H-468-L).

(*c*).—Modified erisophake, with suction needle inserted into the luer lock terminal of the B.D. adapter.

I have now designed a modified form of the Bell erisophake which has several advantages in use. The original instrument was too light to handle with precision, and too short to manipulate. I have therefore added a B.D. adapter (H-468-L) which gives length and manoeuvrability to the instrument. The weight is now much the same as that of eye-scissors and forceps, and the added weight is centralized to act as a fulcrum for the manipulation and extraction of the lens, once the suction has been applied. This luer lock terminal allows the suction needle to be more easily removed for cleaning or storage.

REFERENCES

DIMITRY, T. J. (1933). *Arch. Ophthal. Chicago*, **9**, 261.
HULEN, V. H. (1911). *J. Amer. med. Assoc.*, **57**, 188.
NUGENT, O. B., and FISHER, W. A. (1933). *Illinois med. J.*, **64**, 320.

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† Presented before the West Virginia Academy of Ophthalmology and Otolaryngology, May 13, 1952.

NOTES

PROFESSOR LINDNER

On January 19, 1953, Professor Karl D. Lindner celebrates his 70th birthday. Born in Vienna, he was educated at the Universities of Vienna and Paris, and began his ophthalmological training thereafter in the clinic of Ernst Fuchs. On the retirement of Fuchs, Lindner became an assistant to Dimmer; in 1924 he took charge of the ophthalmological section at the *Poliklinik* in Vienna, and in 1927 succeeded Dimmer as head of the Second University Eye Clinic.

Lindner's scientific investigations have touched on many aspects of ophthalmology; his early work was mainly bacteriological and for his researches on trachoma he received the Von Graefe Prize from the German Ophthalmological Society (1911–1913). In a further important contribution, which concerned refraction, he insisted on the value of retinoscopy with cylinders and introduced refinements into the method of velonoskiascopy.

His experimental and clinical papers on retinal detachment are well known, besides his early work on scleral resection and his introduction of the Lochbrille now used in most clinics throughout the world.

All through his life Lindner has been a pioneer in the use of new operative techniques. Latterly his interests have centred in the problem of the pathogenesis of myopia. A concise idea of his scientific work is most readily obtained from his " Text-book of Ophthalmology ".

OPHTHALMOLOGICAL SOCIETY OF AUSTRALIA (B.M.A.)

Twelfth Annual General and Scientific Meeting, 1952

This meeting was held in Melbourne, in conjunction with the Australasian Medical Congress, from August 21–30, 1952. Dr. George A. Brew, President of the O.S.A., was in charge of the business meetings, and Dr. James A. Flynn presided at the scientific sessions. The Chancellor of the University of Melbourne, Sir Charles Lowe, conferred the honorary degree of M.D. upon two visitors from overseas, Dr. A. B. Reese (*New York*), and Mr. John Foster (*London*), and also upon Dr. Norman McAlister Gregg (*Sydney*).

The Presidential Address was on " Eclipse Blindness—Prevention is Better than Cure ". Dr. Reese delivered papers on " Our Present Concept of Primary Glaucoma ", " Melanosis of the Conjunctiva ", and " Trends in Cataract Surgery ". Mr. Foster's paper on " The Practitioner's Guide to the Fundus Oculi " was attended by final year medical students who requested an encore; his other addresses were entitled " Curiosa Ophthalmica " and " The Büdinger-Müller Operation ". At the request of the late Dr. Cedric Cohen, Mr. Foster also gave a demonstration of " Gadgets " which was of great practical value. Whilst in Sydney he gave another address entitled " A European Colonnade ", and in Adelaide he spoke on " The Time Factor in Ophthalmology ". Mr. Foster has arranged for a paper by Dr. Alfredo Arruga to appear in the Transactions instead of his talk on " Ridley's Lenticulus Operation ", a decision which has been greatly appreciated in Australia.

On behalf of the American Academy of Ophthalmology and Otolaryngology, Dr. Reese presented a motion picture entitled " Embryology of the Eye ", which was made by Dr. George W. Corner (*Baltimore*), and Dr. George Sinclair (*New York*). Professor Ida Mann expressed her own admiration of this film, and the gratitude of members of the O.S.A.

Professor Mann herself delivered an address of unusual importance entitled " The Changing Attitude to Developmental Anomalies ". Other papers were " Observations on the Eye of the Monotremes " by Kevin O'Day, " Investigations into the Blood Supply of the Optic Nerve " by John L. Bignell, " The Advantages of General Anaesthesia in Ophthalmology " by T. a'B. Travers, G. Housman, and K. Galbally, and " Dacryocystorhinostomy " by T. Boyd Law.

IRISH OPHTHALMOLOGICAL SOCIETY

Annual Meeting, 1953

The Annual Meeting of the Irish Ophthalmological Society will be held at the Royal Victoria Eye and Ear Hospital, Dublin, on April 16 and 17, 1953.

L. B. Somerville-Large (*Hon. Sec.*)

OXFORD OPHTHALMOLOGICAL CONGRESS, 1953

The next meeting will be held at Oxford on July 6, 7, and 8, in the Sir William Dunn School of Pathology. Members will be accommodated in Balliol College. Those wishing to read papers should communicate with the Hon. Sec., I. C. Fraser, 21, Dogpole, Shrewsbury.

ROYAL EYE HOSPITAL CLINICAL SOCIETY

The January meeting will be held at the Royal College of Surgeons on Wednesday, January 28, 1953, at 8.0 p.m., when a demonstration of the work of the Ophthalmological Research Unit of the Royal Eye Hospital and the Royal College of Surgeons will be given by the staff.

Supper at 5*s.* 6*d.* will be served at 7.0 p.m. at the Refectory of the College. As accommodation is limited those who wish to take supper are asked to inform the Secretaries of the Society at the Royal Eye Hospital, St. George's Circus, S.E.1., by Saturday, January 24, 1953.

Mr. Harold Ridley, F.R.C.S., has received the Honorary Diploma of Fellowship of the International College of Surgeons.

UNIVERSITY OF TORONTO

REFRESHER COURSE IN EYE SURGERY, 1953

THE Faculty of Medicine is holding a refresher course in Eye Surgery from April 13–17, 1953. The guest surgeons will be Dr. Dohrmann K. Pischel (*San Francisco*) and Mr. H. B. Stallard (*London*). The course will comprise lectures, operative clinics, and cadaver surgery in small groups. The staff of the Department of Ophthalmology in the University will contribute extensively to the course, which will be given for a minimum of ten and a maximum of thirty students.

BRITISH JOURNAL OF OPHTHALMOLOGY CO., LTD.

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XVI INTERNATIONAL CONGRESS OF OPHTHALMOLOGY

THE account books of the above Congress have now been closed and the accounts finally audited. The Executive Committee are happy to state that no call will have to be made upon the guarantors, whom they take this opportunity of thanking very cordially for their generous action in guaranteeing money against a possible loss.

FRANK W. LAW (*Sec.-Gen.*)